INHIBITORS OF INTERLEUKIN-1ß CONVERTING ENZYME

TECHNICAL FIELD OF THE INVENTION

5   The present invention relates to novel classes of compounds which are inhibitors of interleukin-1ß converting enzyme ("ICE"). The ICE inhibitors of this invention are characterized by specific structural and physicochemical features. This invention also relates to pharmaceutical compositions

10   comprising these compounds. The compounds and pharmaceutical compositions of this invention are particularly well suited for inhibiting ICE activity and consequently, may be advantageously used as agents against interleukin-1 ("IL-1") mediated diseases,

15   including inflammatory diseases, autoimmune diseases and neurodegenerative diseases. This invention also relates to methods for inhibiting ICE activity and methods for treating interleukin-1 mediated diseases using the compounds and compositions of this invention.

20   BACKGROUND OF THE INVENTION

         Interleukin 1 ("IL-1") is a major pro-inflammatory and immunoregulatory protein that stimulates fibroblast differentiation and proliferation, the production of prostaglandins,

25   collagenase and phospholipase by synovial cells and chondrocytes, basophil and eosinophil degranulation and

neutrophil activation. Oppenheim, J.H. et al, _Immunology Today_, 7, pp. 45-56 (1986). As such, it is involved in the pathogenesis of chronic and acute inflammatory and autoimmune diseases. IL-1 is

5 predominantly produced by peripheral blood monocytes as part of the inflammatory response and exists in two distinct agonist forms, IL-1α and IL-1ß. Mosely, B.S. et al., _Proc. Nat. Acad. Sci._, 84, pp. 4572-4576 (1987); Lonnemann, G. et al., _Eur.J. Immunol._, 19,

10 pp. 1531-1536 (1989).

IL-1ß is synthesized as a biologically inactive precursor, pIL-1ß. pIL-1ß lacks a conventional leader sequence and is not processed by a ·signal peptidase. March, C.J., _Nature_, 315,

15 pp. 641-647 (1985). Instead, pIL-1ß is cleaved by interleukin-1ß converting enzyme ("ICE") between Asp-116 and Ala-117 to produce the biologically active C-terminal fragment found in human serum and synovial fluid. Sleath, P.R., et al., _J. Biol. Chem._, 265,

20 pp. 14526-14528 (1992); A.D. Howard et al., _J. Immunol._, 147, pp. 2964-2969 (1991). Processing by ICE is also necessary for the transport of mature IL-1ß through the cell membrane.

ICE is a cysteine protease localized

25 primarily in monocytes. It converts precursor IL-1ß to the mature form. Black, R.A. et al., _FEBS Lett._, 247, pp. 386-390 (1989); Kostura, M.J. et al., _Proc. Natl. Acad. Sci. USA_, 86, pp. 5227-5231 (1989). ICE, or its homologues, also appears to be involved in the

30 regulation of cell death or apoptosis. Yuan, J. et al., _Cell_, 75, pp. 641-652 (1993); Miura, M. et al., _Cell_, 75, pp. 653-660 (1993); Nett-Fiordalisi, M.A. et al., _J. Cell Biochem._, 17B, p. 117 (1993). In particular, ICE or ICE homologues are thought to be

35 associated with the regulation of apoptosis in

neurogenerative diseases, such as Alzheimer's and
Parkinson's disease. Marx, J. and M. Baringa, Science,
259, pp. 760-762 (1993); Gagliardini, V. et al.,
Science, 263, pp. 826-828 (1994).

5   ICE has been previously described as a
heterodimer composed of two subunits, p20 and p10
(20kDa and 10kDa molecular weight, respectively).
These subunits are derived from a 45kDa proenzyme (p45)
by way of a p30 form, through an activation mechanism
10   that is autocatalytic. Thornberry, N.A. et al.,
Nature, 356, pp. 768-774 (1992). The ICE proenzyme has
been divided into several functional domains: a
prodomain (p14), a p22/20 subunit, a polypeptide linker
and a p10 subunit. Thornberry et al., supra; Casano
15   et al., Genomics, 20, pp. 474-481 (1994).

Full length p45 has been characterized by its
cDNA and amino acid sequences. PCT patent applications
WO 91/15577 and WO 94/00154. The p20 and p10 cDNA and
amino acid sequences are also known. Thornberry
20   et al., supra. Murine and rat ICE have also been
sequenced and cloned. They have high amino acid and
nucleic acid sequence homology to human ICE. Miller,
D.K. et al., Ann. N.Y. Acad. Sci., 696, pp. 133-148
(1993); Molineaux, S.M. et al., Proc. Nat. Acad. Sci.,
25   90, pp. 1809-1813 (1993). Knowledge of the primary
structure of ICE, however, does not allow prediction of
its tertiary structure. Nor does it afford an
understanding of the structural, conformational and
chemical interactions of ICE and its substrate pIL-1ß
30   or other substrates or inhibitors.

ICE inhibitors represent a class of compounds
useful for the control of inflammation or apoptosis or
both. Peptide and peptidyl inhibitors of ICE have been
described. PCT patent applications WO 91/15577; WO
35   93/05071; WO 93/09135; WO 93/14777 and WO 93/16710; and

European patent application 0 547 699. However, due to
their peptidic nature, such inhibitors are typically
characterized by undesirable pharmacologic properties,
such as poor oral absorption, poor stability and rapid
metabolism. Plattner, J.J. and D.W. Norbeck, in Drug
Discovery Technologies, C.R. Clark and W.H. Moos, Eds.
(Ellis Horwood, Chichester, England, 1990), pp. 92-126.
This has hampered their development into effective
drugs.

Accordingly, the need exists for compounds that
can effectively inhibit the action of ICE, for use as
agents for preventing and treating chronic and acute
forms of IL-1 mediated diseases, including various
cancers, as well as inflammatory, autoimmune or
neurodegenerative diseases.

SUMMARY OF THE INVENTION

The present invention provides novel classes
of compounds, and pharmaceutically acceptable
derivatives thereof, that are useful as inhibitors of
ICE. These compounds can be used alone or in
combination with other therapeutic or prophylactic
agents, such as antibiotics, immunomodulators or other
anti-inflammatory agents, for the treatment or
prophylaxis of diseases mediated by IL-1. According to
a preferred embodiment, the compounds of this invention
are capable of binding to the active site of ICE and
inhibiting the activity of that enzyme.

It is a principal object of this invention to
provide novel classes of inhibitors of ICE. These
novel classes of ICE inhibitors are characterized by
the following structural and physicochemical features:

a)   a first and a second hydrogen
bonding moiety, each of said moieties being capable of
forming a hydrogen bond with a different backbone atom

of ICE, said backbone atom being selected from the group consisting of the carbonyl oxygen of Arg-341, the amide -NH- group of Arg-341, the carbonyl oxygen of Ser-339 and the amide -NH- group of Ser-339;

5   b)   a first and a second moderately hydrophobic moiety, said moieties each being capable of associating with a separate binding pocket of ICE when the inhibitor is bound thereto, said binding pocket being selected from the group consisting of the P2

10   binding pocket, the P3 binding pocket, the P4 binding pocket and the P' binding pocket; and

          c)   an electronegative moiety comprising one or more electronegative atoms, said atoms being attached to the same atom or to adjacent

15   atoms in the moiety and said moiety being capable of forming one or more hydrogen bonds or salt bridges with residues in the P1 binding pocket of ICE.

       It is also an object of this invention to provide a method for identification, design or

20   prediction of ICE inhibitors comprising the steps of:

          a)   selecting a candidate compound of defined chemical structure comprising at least two hydrogen bonding moieties, at least two moderately hydrophobic moieties and one electronegative moiety

25   comprising one or more electronegative atoms attached either to the same atom or to adjacent atoms in the electronegative moiety;

          b)   determining a low-energy conformation for binding of said compound to the active site of ICE;

30   c)   evaluating the capability of said compound in said conformation to form at least two hydrogen bonds with the non-carbon backbone atoms of Arg-341 and Ser-339 of ICE;

          d)   evaluating the capability of said

35   compound in said conformation to associate with at

least two of the binding pockets of ICE selected from the group consisting of the P2 binding pocket, the P3 binding pocket, the P4 binding pocket and the P' binding pocket;

       e)   evaluating the capability of said compound in said conformation to interact with the P1 binding pocket of ICE; and

       f)   accepting or rejecting said candidate compound as an ICE inhibitor based on the determinations and evaluations carried out in the preceding steps.

It is a further object of this invention to provide novel classes of ICE inhibitors represented by formulas:

α

$$R_1-NH-X_1\Big\langle \begin{array}{l} (CJ_2)_m-T \\ (CH_2)_q-R_3 \end{array}$$,

α

,

$\amalg$

,

$\curlyvee$

, and

δ

.
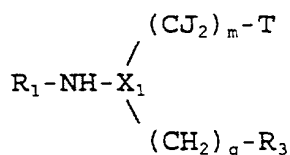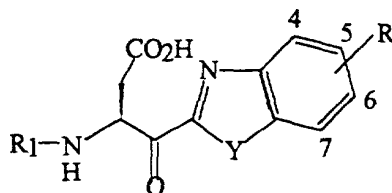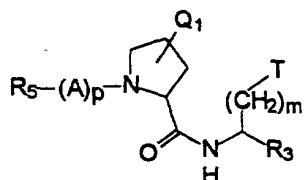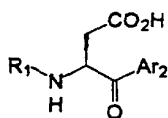
ABBREVIATIONS AND DEFINITIONS

Abbreviations

Designation	Reagent or Fragment
Ala	alanine
Arg	arginine
Asn	asparagine
Asp	aspartic acid
Cys	cysteine
Gln	glutamine
Glu	glutamic acid
Gly	glycine
His	histidine
Ile	isoleucine
Leu	leucine
Lys	lysine
Met	methionine
Phe	phenylalanine
Pro	proline
Ser	serine
Thr	threonine
Trp	tryptophan
Tyr	tyrosine
Val	valine.

Definitions

The following terms are employed herein:

The term "active site" refers to any or all of the following sites in ICE: the substrate binding site, the site where an inhibitor binds and the site where the cleavage of substrate occurs. The active site is characterized by at least amino acid residues: 173, 176, 177, 178, 179, 180, 236, 237, 238, 239, 244, 248, 283, 284, 285, 290, 338, 339, 340, 341, 342, 343,

344, 345, 348, 352, 381, 383, using the sequence and numbering according to Thornberry et al., supra.

The terms "P binding pocket", "S subsite", "S pocket", and the like, refer to binding subsites, or portions of the substrate binding site on the ICE molecule. The amino acid residues of the substrate are given designations according to their position relative to the scissile bond, i.e. the bond which is broken by the protease. The residues are designated P1, P2, etc., for those extending toward the N-terminus of the substrate and P1', P2', etc., for those extending toward the C-terminus of the substrate. The portions of an inhibitor which correspond to the P or P' residues of the substrate are also labeled P1, P1', etc., by analogy with the substrate. The binding subsites of the ICE molecule which receive the residues labeled P1, P1', etc., are designated S1, S1', etc., or may alternately be designated "the P1 binding pocket", "the P1' binding pocket", etc. [I. Schechter and A. Berger, "On the Size of the Active Site in Proteases", Biochem. Biophys. Res. Commun., vol. 27, pp. 157-162 (1967).]

The terms "P2 binding pocket" or "S2 subsite" of the ICE active site are equivalent and are defined as the space surrounded by amino acid residues Pro-290, Val-338 or Trp-340.

The terms "P3 binding pocket" or "S3 subsite" of the ICE active site are equivalent and are defined as the space surrounded by amino acid residues Pro-177, Arg-178, Thr-180, Arg-341 or Pro-343.

The terms "P4 binding pocket" or "S4 subsite" of the ICE active site are equivalent and are defined as the space surrounded by amino acid residues His-342, Met-345, Val-348, Arg-352, Asp-381, Arg-383 or Trp-340.

The terms "P1 binding pocket" or "S1 subsite" of the ICE active site are equivalent and are defined as the space surrounded by amino acid residues Arg-179, His-237, Gln-283, or Arg-341.

5   The terms "P' binding pocket" or "S' subsite" of the ICE active site are equivalent and are defined as the space surrounded by amino acid residues Phe-173, Ile-176, His-237, Gly-238, Ile-239, Cys-244 or His-248.

The term "hydrophobic" refers to a moiety

10   which tends not to dissolve in water and is fat-soluble. Hydrophobic moieties include, but are not limited to, hydrocarbons, such as alkanes, alkenes, alkynes, cycloalkanes, cycloalkenes, cycloalkynes and aromatic compounds, such as aryls, certain saturated

15   and unsaturated heterocycles and moieties that are substantially similar to the side chains of hydrophobic natural and unnatural α-amino acids, including valine, leucine, isoleucine, methionine, phenylanine, α-amino isobutyric acid, alloisoleucine, tyrosine, and

20   tryptophan.

The term "moderately hydrophobic" refers to a hydrophobic moiety in which one or two carbon atoms have been replaced with more polar atoms, such as oxygen or nitrogen.

25   The term "heterocycle" or "heterocyclic" refers to a stable mono- or polycyclic compound which may optionally contain one or two double bonds or may optionally contain one or more aromatic rings. Each heterocycle consists of carbon atoms and from one to

30   four heteroatoms independently selected from a group including nitrogen, oxygen, and sulfur. As used herein, the terms "nitrogen heteroatoms" and "sulphur heteroatoms" include any oxidized form of nitrogen or sulfur and the quaternized form of any basic nitrogen.

35   Heterocycles defined above include, for example,

pyrimidinyl, tetrahydroquinolyl,
tetrahydroisoquinonlinyl, purinyl, pyrimidyl,
indolinyl, benzimidazolyl, imidazolyl, imidazolinoyl,
imidazolidinyl, quinolyl, isoquinolyl, indolyl,
pyridyl, pyrrolyl, pyrrolinyl, pyrazolyl, pyrazinyl,
quinoxolyl, piperidinyl, morpholinyl, thiamorpholinyl,
furyl, thienyl, triazolyl, thiazolyl, ß-carbolinyl,
tetrazolyl, thiazolidinyl, benzofuranoyl,
thiamorpholinyl sulfone, benzoxazolyl, oxopiperidinyl,
oxopyrroldinyl, oxoazepinyl, azepinyl, isoxazolyl,
tetrahydropyranyl, tetrahydrofuranyl, thiadiazolyl,
benzodioxolyl, benzothienyl, tetrahydrothiophenyl and
sulfolanyl. Further heterocycles are described in A.R.
Katritzky and C.W. Rees, eds., Comprehensive
Heterocyclic Chemistry: The Structure, Reactions,
Synthesis and Use of Heterocyclic Compounds, Vol. 1-8,
Pergamon Press, NY (1984).

The term "cycloalkyl" refers to a mono- or
polycyclic group which contains 3 to 15 carbons and may
optionally contain one or two double bonds. Examples
include cyclohexyl, adamantyl and norbornyl.

The term "aryl" refers to a mono- or
polycyclic group which contains 6, 10, 12, or 14
carbons in which at least one ring is aromatic.
Examples include phenyl, naphthyl and biphenyl.

The term "heteroaromatic" refers to a mono-
or polycyclic group which contains 1 to 15 carbon atoms
and from 1 to 4 heteroatoms, each of which is selected
independently from a group including sulphur, nitrogen
and oxygen, and which additionally contains from 1 to 3
five or six membered rings, at least one of which is
aromatic.

The term "alpha-amino acid" (α-amino acid)
refers to both the naturally occurring amino acids and
other "non-protein" α-amino acids commonly utilized by

those in the peptide chemistry arts when preparing synthetic analogues of naturally occurring peptides, including D and L forms. The naturally occurring amino acids are glycine, alanine, valine, leucine, iso-

5   leucine, serine, methionine, threonine, phenylalanine, tyrosine, tryptophan, cysteine, proline, histidine, aspartic acid, asparagine, glutamic acid, glutamine, γ-carboxyglutamic acid, arginine, ornithine and lysine. Examples of "non-protein" alpha-amino acids include

10   hydroxylysine, homoserine, homotyrosine, homo-phenylalanine, citrulline, kynurenine, 4-amino-phenylalanine, 3-(2-naphthyl)-alanine, 3-(1-naphthyl)-alanine, methionine sulfone, t-butyl-alanine, t-butylglycine, 4-hydroxyphenylglycine, aminoalanine,

15   phenylglycine, vinylalanine, propargyl-glycine, 1,2,4-triazolo-3-alanine, 4,4,4-trifluoro-threonine, thyronine, 6-hydroxytryptophan, 5-hydro-xytryptophan, 3-hydroxykynurenine, 3-aminotyrosine, trifuoromethyl-alanine, 2-thienylalanine, (2-(4-pyridyl)ethyl)-

20   cysteine, 3,4-dimethoxy-phenylalanine, 3-(2-thiazolyl)-alanine, ibotenic acid, 1-amino-1-cyclopentane-carboxylic acid, 1-amino-1-cyclohexanecarboxylic acid, quisqualic acid, 3-trifuoromethylphenylalanine, 4-trifuoro-methylphenylalanine, cyclohexylalanine,

25   cyclo-hexylglycine, thiohistidine, 3-methoxytyrosine, elastatinal, norleucine, norvaline, alloisoleucine, homoarginine, thioproline, dehydroproline, hydroxy-proline, isonipectotic acid, homoproline, cyclohexyl-glycine, α-amino-n-butyric acid, cyclohexylalanine,

30   aminophenylbutyric acid, phenylalanines substituted at the ortho, meta, or para position of the phenyl moiety with one or two of the following: a (C_1-C_4) alkyl, a (C_1-C_4) alkoxy, halogen or nitro groups or substituted with a methylenedioxy group; ß-2- and 3-thienyl-

35   alanine, ß-2- and 3-furanylalanine, ß-2-, 3- and

4-pyridylalanine, ß-(benzothienyl-2- and 3-yl)alanine, ß-(1- and 2-naphthyl)alanine, O-alkylated derivatives of serine, threonine or tyrosine, S-alkylated cysteine, S-alkylated homocysteine, O-sulfate, O-phosphate and O-carboxylate esters of tyrosine, 3-sulfo-tyrosine, 3-carboxy-tyrosine, 3-phospho-tyrosine, 4-methane sulfonic acid ester of tyrosine, 4-methane phosphonic acid ester of tyrosine, 3,5-diiodotyrosine, 3-nitro-tyrosine, ε-alkyl lysine, and delta-alkyl ornithine. Any of these α-amino acids may be substituted with a methyl group at the alpha position, a halogen at any aromatic residue on the α-amino side chain, or an appropriate protective group at the O, N, or S atoms of the side chain residues. Appropriate protective groups are disclosed in "Protective Groups In Organic Synthesis," T.W. Greene and P.G.M. Wuts, J. Wiley & Sons, NY, NY, 1991.

The term "α-amino acid side chain residue" refers to a chemical moiety which is attached to the α-carbon of an alpha-amino acid.

The term "bioisosteric replacement for -CO$_2$H" refers to group which may substitute for a carboxylic acid group in bioactive molecules. Examples of such groups are disclosed in Christopher A. Lipinski, "Bioisosteres in Drug Design" Annual Reports In Medical Chemistry, 21, pp. 286-88 (1986), and in C.W. Thornber, "Isosterism and Molecular Modification in Drug Design" Chemical Society Reviews, pp. 563-580 (1979).

The term "association" is used in reference to a condition of proximity between an inhibitor or portions thereof to an ICE molecule or portions thereof wherein the juxtaposition is energetically favored by electrostatic or van der Waals interactions.

The term "hydrogen bond" refers to a favorable interaction that occurs whenever a suitable

donor atom, X, bearing a proton, H, and a suitable
acceptor atom, Y, have a separation of between 2.5Å and
3.5Å and where the angle X-H - - - Y is greater than 90
degrees. Suitable donor and acceptor atoms are well

5   understood in medicinal chemistry (G.C. Pimentel and
A.L. McClellan, The Hydrogen Bond, Freeman, San
Francisco, 1960; R. Taylor and O. Kennard, "Hydrogen
Bond Geometry in Organic Crystals", Accounts of
Chemical Research, 17, pp. 320-326 (1984)).

10   The term "salt bridge" refers to the non-
covalent attractive interaction between a positively
charged moiety (P) and a negatively charged moiety (N)
when the distance between the centers of mass of P and
N is between 2 and 6 Angstroms. In calculating the

15   center of mass, atoms which may contain a formal charge
and atoms immediately adjacent to these are included.
For example, a salt bridge may be formed between the
positively charged guanidinium side chain of an
arginine residue and the negative charged carboxylate

20   side chain of a glutamate residue. Salt bridges are
well understood in medicinal chemistry (L. Stryer,
Biochemistry, Freeman, San Francisco, (1975);
K.A. Dill, "Dominant Forces in Protein Folding",
Biochemistry, 29, No. 31, pp. 7133-7155, (1990)).

25   The term "center of mass" refers to a point
in three-dimensional space which represents a weighted
average position of the masses that make up an object.

          The terms "backbone chain" and "backbone"
refer to the portion of a polypeptide which comprises

30   the repeating unit -CO-CH-NH-.

          The term "scaffold" refers to a structural
building block which forms the basis of an ICE
inhibitor according to this invention. Various
moieties and functional groups are intended to be

35   appended to the scaffold. The scaffolds of this

invention are thus depicted having open valences.
Various scaffolds of ICE inhibitors according to this
invention include the portions:

5 .
$$\begin{array}{c} X \\ \backslash \; / \; \backslash \; / \\ N \qquad C \\ | \qquad \| \\ H \qquad O \end{array}$$

or

10
$$\begin{array}{c} X \\ \backslash \; / \; \backslash \; / \\ N \qquad SO \\ | \qquad \| \\ H \qquad O \end{array} \qquad .$$

15   In those scaffolds, the NH and CO or SO_2 moieties
represent a first and a second hydrogen bonding moiety,
said moieties each being capable of forming a hydrogen
bond with a backbone atom of ICE, said backbone atom
being selected from the group consisting of the
20   carbonyl oxygen of Arg-341, the amide -NH- of Arg-341,
the carbonyl oxygen of Ser-339 and the amide -NH- of
Ser-339.

The term "substitute" refers to the
replacement of a hydrogen atom in a compound with a
25   substituent group. In the present invention, those
hydrogen atoms which form a part of a hydrogen bonding
moiety which is capable of forming a hydrogen bond with
the carbonyl oxygen of Arg-341 of ICE or the carbonyl
oxygen of Ser-339 of ICE are excluded from
30   substitution. These excluded hydrogen atoms include
those which comprise an -NH- group which is alpha to a
Z or a -CO- group and are depicted as -NH- rather than
an X group or some other designation in the following
diagrams: (a) through (t), (v) through (y), and (I)
35   through (VIID).

The term "straight chain" refers to a contiguous unbranching string of covalently bound members, i.e. atoms, which form a portion of a ring. The straight chain and the ring of which it forms a part may be substituted, but these substituents are not a part of the straight chain.

The term "K_i" refers to a numerical measure of the effectiveness of a compound in inhibiting the activity of a target enzyme such as ICE. Lower values of K_i reflect higher effectiveness. The K_i value is a derived by fitting experimentally determined rate data to standard enzyme kinetic equations (see I. H. Segel, Enzyme Kinetics, Wiley-Interscience, 1975).

The term "minimize" refers to the systematic altering of the atomic geometry of a molecule or molecular complex so that any further minor perturbation of the atomic geometry would cause the total energy of the system as measured by a molecular mechanics force-field to increase. Minimization and molecular mechanics force-fields are well understood in computational chemistry [U. Burkert and N.L. Allinger, Molecular Mechanics, ACS Monograph 177, American Chemical Society, Washington, D.C. 1982 pages 59-78].

The term "strain energy" is used in this application to refer to the difference between the free conformation energy of a compound and the bound conformation energy of that compound when bound to ICE. The strain energy can be determined by the following steps: Evaluate the energy of the molecule when it has the conformation necessary for binding to ICE. Then minimize and reevaluate the energy -- this is the free conformation energy. The strain energy for binding of a potential inhibitor to ICE is the difference between the free conformation energy and the bound conformation energy. In a preferred embodiment, the strain energy

of an inhibitor of the present invention is less than about 10 kcal/mol.

The term "patient" as used in this application refers to any mammal, especially humans.

The term "pharmaceutically effective amount" refers to an amount effective in treating or ameliorating an IL-1 mediated disease in a patient. The term "prophylactically effective amount" refers to an amount effective in preventing or substantially lessening IL-1 mediated disease in a patient.

The term "pharmaceutically acceptable carrier or adjuvant" refers to a non-toxic carrier or adjuvant that may be administered to a patient, together with a compound of this invention, and which does not destroy the pharmacological activity thereof.

The term "pharmaceutically acceptable derivative" means any pharmaceutically acceptable salt, ester, or salt of such ester, of a compound of this invention or any other compound which, upon administration to a recipient, is capable of providing (directly or indirectly) a compound of this invention or an anti-ICE active metabolite or residue thereof.

Pharmaceutically acceptable salts of the compounds of this invention include, for example, those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acids include hydrochloric, hydrobromic, sulfuric, nitric, perchloric, fumaric, maleic, phosphoric, glycolic, lactic, salicylic, succinic, toluene-p-sulfonic, tartaric, acetic, citric, methanesulfonic, formic, benzoic, malonic, naphthalene-2-sulfonic and benzenesulfonic acids. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds of the

invention and their pharmaceutically acceptable acid addition salts. Salts derived from appropriate bases include alkali metal (e.g., sodium), alkaline earth metal (e.g., magnesium), ammonium and $N-(C_{1-4} \text{ alkyl})_4^+$ salts.

This invention also envisions the "quaternization" of any basic nitrogen-containing groups of the compounds disclosed herein. The basic nitrogen can be quaternized with any agents known to those of ordinary skill in the art including, for example, lower alkyl halides, such as methyl, ethyl, propyl and butyl chloride, bromides and iodides; dialkyl sulfates including dimethyl, diethyl, dibutyl and diamyl sulfates; long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides; and aralkyl halides including benzyl and phenethyl bromides. Water or oil-soluble or dispersible products may be obtained by such quaternization.

The ICE inhibitors of this invention may contain one or more "asymmetric" carbon atoms and thus may occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. All such isomeric forms of these compounds are expressly included in the present invention. Each stereogenic carbon may be of the R or S configuration. Although specific compounds and scaffolds exemplified in this application may be depicted in a particular stereochemical configuration, compounds and scaffolds having either the opposite stereochemistry at any given chiral center or mixtures thereof are also envisioned.

The ICE inhibitors of this invention may comprise ring structures which may optionally be substituted at carbon, nitrogen or other atoms by

various substituents. Such ring structures may be
singly or multiply substituted. Preferably, the ring
structures contain between 0 and 3 substituents. When
multiply substituted, each substituent may be picked
independently of any other substituent as long as the
combination of substituents results in the formation of
a stable compound.

Combinations of substituents and variables
envisioned by this invention are only those that result
in the formation of stable compounds. The term
"stable", as used herein, refers to compounds which
possess stability sufficient to allow manufacture and
administration to a mammal by methods known in the art.
Typically, such compounds are stable at a temperature
of 40°C or less, in the absence of moisture or other
chemically reactive conditions, for at least a week.

DETAILED DESCRIPTION OF THE INVENTION

In order that the invention herein described
may be more fully understood, the following detailed
description is set forth.

We have discovered that compounds possessing
the following novel combination of features are
surprisingly effective ICE inhibitors:

a)   a first and a second hydrogen bonding
moiety, each of said moieties being capable of forming
a hydrogen bond with a different backbone atom of ICE,
said backbone atom being selected from the group
consisting of the carbonyl oxygen of Arg-341, the amide
-NH- group of Arg-341, the carbonyl oxygen of Ser-339
and the amide -NH- group of Ser-339;

b)   a first and a second moderately
hydrophobic moiety, said moieties each being capable of
associating with a separate binding pocket of ICE when
the inhibitor is bound thereto, said binding pocket

being selected from the group consisting of the P2 binding pocket, the P3 binding pocket, the P4 binding pocket and the P' binding pocket; and

      c)   an electronegative moiety comprising one or more electronegative atoms, said atoms being attached to the same atom or to adjacent atoms in the moiety and said moiety being capable of forming one or more hydrogen bonds or salt bridges with residues in the P1 binding pocket of ICE.

      Preferably, any moderately hydrophobic moiety associating with the P2 binding pocket of ICE does so in such a way that:

      a)   the distance from the center of mass of the moderately hydrophobic moiety in the P2 binding pocket to the carbonyl oxygen of Arg-341 of ICE is between about 7.1Å and about 12.5Å;

      b)   the distance from the center of mass of the moderately hydrophobic moiety in the P2 binding pocket to the amide nitrogen of Arg-341 of ICE is between about 6.0Å and about 12Å; and

      c)   the distance from the center of mass of the moderately hydrophobic moiety in the P2 binding pocket to the carbonyl oxygen of Ser-339 of ICE is between about 3.7Å and about 9.5Å.

      Preferably, any moderately hydrophobic moiety associating with the P3 binding pocket of ICE does so in such a way that:

      a)   the distance from the center of mass of the moderately hydrophobic moiety in the P3 binding pocket to the carbonyl oxygen of Arg-341 of ICE is between about 3.9Å and about 9.5Å;

      b)   the distance from the center of mass of the moderately hydrophobic moiety in the P3 binding pocket to the amide nitrogen of Arg-341 of ICE is between about 5.4Å and about 11Å; and

c)   the distance from the center of
mass of the moderately hydrophobic moiety in the P3
binding pocket to the carbonyl oxygen of Ser-339 of ICE
is between about 7.0Å and about 13Å.

Preferably, any moderately hydrophobic moiety
associating with the P4 binding pocket of ICE does so
in such a way that:

a)   the distance from the center of
mass of the moderately hydrophobic moiety in the P4
binding pocket to the carbonyl oxygen of Arg-341 of ICE
is between about 4.5Å and about 7.5Å;

b)   the distance from the center of
mass of the moderately hydrophobic moiety in the P4
binding pocket to the amide nitrogen of Arg-341 of ICE
is between about 5.5Å and about 8.5Å; and

c)   the distance from the center of
mass of the moderately hydrophobic moiety in the P4
binding pocket to the carbonyl oxygen of Ser-339 of ICE
is between about 8Å and about 11Å.

Preferably, any moderately hydrophobic moiety
associating with the P' binding pocket of ICE does so
in such a way that:

a)   the distance from the center of
mass of the moderately hydrophobic moiety in the P'
binding pocket to the carbonyl oxygen of Arg-341 of ICE
is between about 11Å and about 16Å;

b)   the distance from the center of
mass of the moderately hydrophobic moiety in the P'
binding pocket to the amide nitrogen of Arg-341 of ICE
is between about 10Å and about 15Å; and

c)   the distance from the center of
mass of the moderately hydrophobic moiety in the P'
binding pocket to the carbonyl oxygen of Ser-339 of ICE
is between about 8Å and about 12Å.

More preferably, all of the above associative conditions are met in the compounds of this invention.

The practitioner skilled in the art will appreciate that there are a number of means to design the inhibitors of the present invention. These same means may be used to select a candidate compound for screening as an ICE inhibitor. This design or selection may begin with selection of the various moieties which fill binding pockets.

There are a number of ways to select moieties to fill individual binding pockets. These include visual inspection of a physical model or computer model of the active site and manual docking of models of selected moieties into various binding pockets. Modeling software that is well known and available in the art may be used. These include QUANTA [Molecular Simulations, Inc., Burlington, MA, 1992], SYBYL [Molecular Modeling Software, Tripos Associates, Inc., St. Louis, MO, 1992], AMBER [S.J. Weiner, P.A. Kollman, D.A. Case, U.C. Singh, C. Ghio, G. Alagona, and P. Weiner, _J. Am. Chem. Soc._, vol. 106, pp. 765-784 (1984)], or CHARMM [B.R. Brooks, R.E. Bruccoleri, B.D. Olafson, D.J. States, S Swaminathan, and M. Karplus, _J. Comp. Chem._ vol. 4, pp. 187-217 (1983)]. This modelling step may be followed by energy minimization with standard molecular mechanics forcefields such as CHARMM and AMBER. In addition, there are a number of more specialized computer programs to assist in the process of selecting the binding moieties of this invention. These include:

    1. GRID (Goodford, P.J. A Computational Procedure for Determining Energetically Favorable Binding Sites on Biologically Important Macromolecules. _J. Med. Chem._, 28, pp. 849-857 (1985)). GRID is available from Oxford University, Oxford, UK.

2. MCSS (Miranker, A.; Karplus, M. Functionality Maps of Binding Sites: A Multiple Copy Simultaneous Search Method. Proteins: Structure, Function and Genetics, 11, pp. 29-34 (1991)). MCSS is available from Molecular Simulations, Burlington, MA.

3. AUTODOCK (Goodsell, D.S.; Olsen, A.J. Automated Docking of Substrates to Proteins by Simmulated Annealing. PROTEINS: Structure, Function and Genetics, 8, pp. 195-202 (1990)). AUTODOCK is available from the Scripps Research Institute, La Jolla, CA.

4. DOCK (Kuntz, I.D.; Blaney, J.M.; Oatley, S.J.; Langridge, R.; Ferrin, T.E. A Geometric Approach to Macromolecule-Ligand Interactions. J. Mol. Biol., 161, pp. 269-288 (1982)). DOCK is available from the University of California, San Francisco, CA.

Once suitable binding moieties have been selected, they can be assembled into a single inhibitor. This assembly may be accomplished by connecting the various moieties to a central scaffold. The assembly process may, for example, be done by visual inspection followed by manual model building, again using software such as Quanta or Sybyl. A number of other programs may also be used to help select ways to connect the various moieties. These include:

1. CAVEAT (Bartlett, P.A.; Shea, G.T.; Telfer, S.J.; Waterman, S. CAVEAT: A Program to Facilitate the Structure-Derived Design of Biologically Active Molecules. In "Molecular Recognition in Chemical and Biological Problems," Special Pub., Royal Chem. Soc., 78, pp. 182-196 (1989)). CAVEAT is available from the University of California, Berkeley, CA.

2. 3D Database systems such as MACCS-3D (MDL Information Systems, San Leandro, CA). This area has been recently reviewed by Martin (Martin, Y.C. 3D Database Searching in Drug Design. J. Med. Chem., 35, pp. 2145-2154 (1992)).

3.   HOOK (available from Molecular
Simulations, Burlington, MA).

        In addition to the above computer assisted
modeling of inhibitor compounds, the inhibitors of this
invention may be constructed "de novo" using either an
empty active site or optionally including some portions
of a known inhibitor. Such methods are well known in
the art. They include, for example:

    1.   LUDI (Bohm, H.J. The Computer Program
    LUDI: A New Method for the De Novo Design of
    Enzyme Inhibitors. <u>J. Comp. Aid. Molec.</u>
    <u>Design.</u>, 6, 61-78 (1992)). LUDI is available
    from Biosym Technologies, San Diego, CA.

    2.   LEGEND (Nishibata, Y., Itai, A.,
    <u>Tetrahedron</u>, 47, 8985 (1991)). LEGEND is
    available from Molecular Simultations,
    Burlington, MA.

    3.   LeapFrog (available from Tripos
    associates, St. Louis, MO).

        A number of techniques commonly used for
modeling drugs may be employed (For a review, see:
Cohen, N.C.; Blaney, J.M.; Humblet, C.; Gund, P.;
Barry, D.C., "Molecular Modeling Software and Methods
for Medicinal Chemistry", <u>J. Med. Chem.</u>, 33, pp. 883-
894 (1990)). There are likewise a number of examples
in the chemical literature of techniques that can be
applied to specific drug design projects. For a
review, see: Navia, M.A. and Murcko, M.A., "The Use of
Structural Information in Drug Design", <u>Current</u>
<u>Opinions in Structural Biology</u>, 2, pp. 202-210 (1992).
Some examples of these specific applications include:
Baldwin, J.J. et al., "Thienothiopyran-2-sulfonamides:
Novel Topically Active Carbonic Anhydrase Inhibitors
for the Treatment of Glaucoma", <u>J. Med. Chem.</u>, 32, pp.
2510-2513 (1989); Appelt, K. et al., "Design of Enzyme
Inhibitors Using Iterative Protein Crystallographic
Analysis", <u>J. Med. Chem.</u>, 34, pp. 1925-1934 (1991); and

Ealick, S.E. et al., "Application of Crystallographic and Modeling Methods in the Design of Purine Nucleotide Phosphorylase Inhibitors" Proc. Nat. Acad. Sci. USA, 88, pp. 11540-11544 (1991).

5   Using the novel combination of steps of the present invention, the skilled artisan can advantageously avoid time consuming and expensive experimentation to determine enzymatic inhibition activity of particular compounds. The method also is
10   useful to facilitate rational design of ICE inhibitors and therapeutic and prophylactic agents against IL-1-mediated diseases. Accordingly, the present invention relates to such inhibitors.

A variety of conventional techniques may be
15   used to carry out each of the above evaluations as well as the evaluations necessary in screening a candidate compound for ICE inhibiting activity. Generally, these techniques involve determining the location and binding proximity of a given moiety, the occupied space of a
20   bound inhibitor, the deformation energy of binding of a given compound and electrostatic interaction energies. Examples of conventional techniques useful in the above evaluations include: quantum mechanics, molecular mechanics, molecular dynamics, Monte Carlo sampling,
25   systematic searches and distance geometry methods (G.R. Marshall, Ann. Ref. Pharmacol. Toxicol., 27, p. 193 (1987)). Specific computer software has been developed for use in carrying out these methods. Examples of programs designed for such uses include: Gaussian 92,
30   revision E.2 (M.J. Frisch, Gaussian, Inc., Pittsburgh, PA ©1993); AMBER, version 4.0 (P.A. Kollman, University of California at San Francisco, ©1993); QUANTA/CHARMM [Molecular Simulations, Inc., Burlington, MA ©1992]; and Insight II/Discover (Biosysm Technologies Inc., San
35   Diego, CA ©1992). These programs may be implemented,

for instance, using a Silicon Graphics Indigo 2
workstation or IBM RISC/6000 workstation model 550.
Other hardware systems and software packages will be
known and of evident applicability to those skilled in
5   the art.

Different classes of active ICE inhibitors,
according to this invention, may interact in similar
ways with the various binding pockets of the ICE active
site. The spatial arrangement of these important
10   groups is often referred to as a pharmacophore. The
concept of the pharmacophore has been well described in
the literature (D. Mayer, C.B. Naylor, I. Motoc, and
G.R. Marshall, J. Comp. Aided Molec. Design vol. 1, pp.
3-16 (1987); A. Hopfinger and B.J. Burke, in Concepts
15   and Applications of Molecular Similarity, M.A. Johnson
and G.M. Maggiora, ed., Wiley (1990)).

Different classes of ICE inhibitors of this
invention may also use different scaffolds or core
structures, but all of these cores will allow the
20   necessary moieties to be placed in the active site such
that the specific interactions necessary for binding
may be obtained. These compounds are best defined in
terms of their ability to match the pharmacophore,
i.e., their structural identity relative to the shape
25   and properties of the active site of ICE.

The ICE inhibitors of one embodiment of this
invention comprise a first and a second hydrogen
bonding moiety, a first and a second moderately
hydrophobic moiety, and an electronegative moiety which
30   comprise or are covalently bound to one of the
following scaffolds:

(I)

$$
\begin{array}{c}
W_1\overset{r}{-}X\overset{r}{-}W_2 \\
X\diagdown\diagup X^r \\
N\diagdown X\diagup X^r \\
\mid\quad\diagdown Z\diagup \\
H
\end{array}
$$

;

(II)

$$N-X \overset{r}{\underset{Z}{\overset{W_3}{\diamond}}} X$$
H

;

5 (III)

$$W_4 \overset{r}{\diamond} X \overset{r}{\overset{W_5}{\diamond}} X \overset{r}{\diamond} W_6$$

;

(IV)

$$W_7 \overset{r}{\diamond} X \overset{r}{\diamond} W_8$$

;

10

(V)

$$W_9 \overset{r}{\diamond} X \overset{W_{10}}{\diamond} X$$

;

15 (VI)

$$W_{11} \overset{r}{\diamond} X - Z - X \overset{r}{\underset{r}{\diamond}} W_{12}$$

; and

(VII)

$$\overset{W_{13}}{N} - X - Z$$
H

.

20

The ICE inhibitors of another embodiment (A)
of this invention are those of formula α:

25 $\underline{\alpha}$

$$R_1-NH-X_1 \overset{(CJ_2)_m-T}{\underset{(CH_2)_g-R_3}{\diamond}}$$,
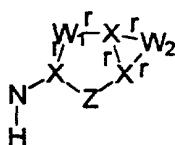
wherein:

X$_1$ is CH or N;

g is 0 or 1;

each J is independently selected from the group consisting of -H, -OH, and -F, provided that when a first and second J are bound to a C and said first J is -OH, said second J is -H;

m is 0, 1, or 2;

T is -Ar$_3$, -OH, -CF$_3$, -CO-CO$_2$H, -CO$_2$H or any bioisosteric replacement for -CO$_2$H;

R$_1$ is selected from the group consisting of the following formulae, in which any ring may optionally be singly or multiply substituted at any carbon by Q$_1$, at any nitrogen by R$_5$, or at any atom by =O, -OH, -CO$_2$H, or halogen, and in which any saturated ring may optionally be unsaturated at one or two bonds:

(a) ;

(b) ;

(C) ;

(d) ;

(e)

$$\text{R}_5\text{—NH—X}_5 \cdots$$

;

(f)

$$\text{R}_5\text{—NH—C—C—R}_{20}\text{—Z—}$$

;

(g)

$$\text{Z—R}_{20}\text{—Z—}$$

;

(h)

$$\text{Z—R}_{20}\text{—Z—}$$

;

(i)

;

(j)

;

(k)

;

(l)

;

(m)

;

(n)

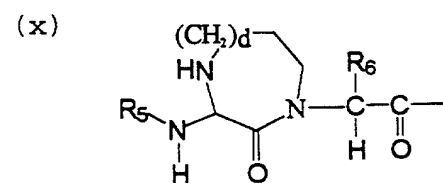
;

5 (o)

;

(p)

;

10

(q)

;

(r)

;

15 (s)

;

(t)

;

20

(v)

;

R_{20} is selected from the group consisting of:

(aa1)

;

(aa2)

;

(aa3)

;

(aa4)

;

(aa5)

;

(bb)

;

(cc)

;

(dd)

;

(ee)

;

(ff)

;

(gg)

;

(gga)

(CH₂)a
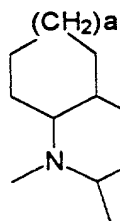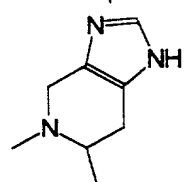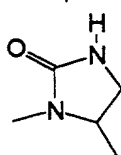

;

(ggb)

; and

(ggc)

;

wherein each ring C is independently chosen from the group consisting of benzo, pyrido, thieno, pyrrolo, furano, thiazolo, isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo, cyclopentyl, and cyclohexyl;

R_3 is

$-CN$,

$-CH=CH-R_9$,

$-CH=N-O-R_9$,

$-(CH_2)_{1-3}-T_1-R_9$,

$-CJ_2-R_9$,

$-CO-R_{13}$, or

$$-CO-CO-N \begin{array}{c} /R_5 \\ \backslash R_{10}; \end{array}$$

each R_4 is independently selected from the group consisting of:

-H,

-Ar_1,

-R_9,

-T_1-R_9, and

-$(CH_2)_{1,2,3}$-T_1-R_9,

each T_1 is independently selected from the group consisting of:

-CH=CH-,

-O-,

-S-,

-SO-,

-SO_2-,

-NR_{10}-,

-NR_{10}-CO-,

-CO-,

-O-CO-,

-CO-O-,

-CO-NR_{10}-,

-O-CO-NR_{10}-,

-NR_{10}-CO-O-,

-NR_{10}-CO-NR_{10}-,

-SO_2-NR_{10}-,

-NR_{10}-SO_2-,   and

-NR_{10}-SO_2-NR_{10}-,

each R_5 is independently selected from the group consisting of:

-H,

-Ar_1,

$-CO-Ar_1$,

$-SO_2-Ar_1$,

$-R_9$,

$-CO-R_9$,

$-CO-O-R_9$,

$-SO_2-R_9$,

$$-CO-N\begin{smallmatrix}/Ar_1\\\backslash R_{10}\end{smallmatrix},$$

$$-SO_2-N\begin{smallmatrix}/Ar_1\\\backslash R_{10}\end{smallmatrix},$$

$$-CO-N\begin{smallmatrix}/R_9\\\backslash R_{10}\end{smallmatrix}, \quad and$$

$$-SO_2-N\begin{smallmatrix}/R_9\\\backslash R_{10}\end{smallmatrix},$$

R_6 and R_7 taken together form a saturated 4-8 member carbocyclic ring or heterocyclic ring containing -O-, -S-, or -NH-, or

R_7 is -H and R_6 is

-H

$-Ar_1$,

$-R_9$, or

$-(CH_2)_{1,2,3}-T_1-R_9$;

each R_9 is a C_{1-6} straight or branched alkyl group optionally singly or multiply substituted by -OH, -F, or =O and optionally substituted with one or two Ar_1 groups;

each R_{10} is independently selected from the group consisting of -H or a C_{1-6} straight or branched alkyl group;

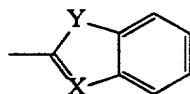each R_{13} is independently selected from the group consisting of -Ar_2 and -R_4;

each Ar_1 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, a cycloalkyl group which contains between 3 and 15 carbon atoms and between 1 and 3 rings, said cycloalkyl group being optionally benzofused, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocycle group containing at least one heteroatom group selected from -O-, -S-, -SO-, -SO_2-, =N-, and -NH-, said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by =O, -OH, perfluoro C_{1-3} alkyl, or -Q_1;
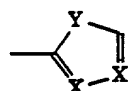
each Ar_2 is independently selected from the following group, in which any ring may optionally be substituted by -Q_1:
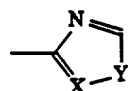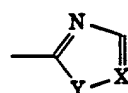
(hh)

;

(ii)

;

(jj)

; and

(kk)
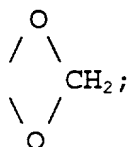

;
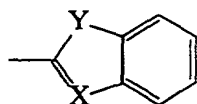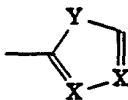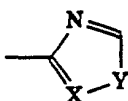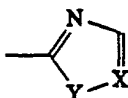
Ar$_3$ is a cyclic group selected from the set consisting of a phenyl ring, a 5-membered heteroaromatic ring, and a 6-membered heteroaromatic ring, said heteroaromatic rings comprising 1-3 heteroatom groups selected from -O-, -S-, -SO-, -SO$_2$-, =N-, and -NH-, said cyclic group optionally being singly or multiply substituted with =O, -OH, halogen, perfluoro C$_{1-3}$ alkyl, or -CO$_2$H;

each Q$_1$ is independently selected from the group consisting of:

-Ar$_1$

-R$_9$,

-T$_1$-R$_9$,   and

- (CH$_2$)$_{1,2,3}$-T$_1$-R$_9$,

provided that when -Ar$_1$ is substituted with a Q$_1$ group which comprises one or more additional -Ar$_1$ groups, said additional -Ar$_1$ groups are not substituted with Q$_1$;

each X is independently selected from the group consisting of =N-, and =CH-;

each X$_2$ is independently selected from the group consisting of -O-, -CH$_2$-, -NH-, -S-, -SO-, and -SO$_2$; each X$_3$ is independently selected from the group consisting of -CH$_2$-, -S-, -SO-, and -SO$_2$-;

each X$_4$ is independently selected from the group consisting of -CH$_2$- and -NH-;

each X$_5$ is independently selected from the group consisting of -CH- and -N-;

X_6 is CH or N, provided that when X_6 is N in the R_1 group labeled (o) and X_5 is CH and X_2 is CH_2 the ring of the R_1 group labeled (o) must be substituted by Q_1 or benzofused;

each Y is independently selected from the group consisting of -O- and -S-;

each Z is independently CO or SO_2,

each a is independently 0 or 1,

each c is independently 1 or 2,

each d is independently 0, 1, or 2, and

each e is independently 0, 1, 2, or 3.

The ICE inhibitors of another embodiment (B) of this invention are those of formula α:

$$\alpha \qquad R_1-NH-X_1 \overset{\displaystyle (CJ_2)_m-T}{\underset{\displaystyle (CH_2)_g-R_3}{<}} \qquad ,$$

wherein:

X_1 is -CH;

g is 0 or 1;

each J is independently selected from the group consisting of -H, -OH, and -F, provided that when a first and second J are bound to a C and said first J is -OH, said second J is -H;

m is 0, 1, or 2;

T is -OH, -CO-CO$_2$H, -CO$_2$H or any bioisosteric replacement for -CO$_2$H;

R$_1$ is selected from the group consisting of the following formulae, in which any ring may optionally be singly or multiply substituted at any carbon by Q$_1$, at any nitrogen by R$_5$, or at any atom by =O, -OH, -CO$_2$H, or halogen, any saturated ring may optionally be unsaturated at one or two bonds; and wherein R$_1$ (e) and R$_1$ (y) are optionally benzofused;

(a)

;

(b)

;

(c)

;

(d)

;

(e)

;

(f)

$$R_5-NH-\underset{R_7}{\overset{R_6}{C}}-\underset{O}{C}-R_{20}-Z-$$;

(g)

$$\begin{array}{c} X-X \\ X \quad Z-R_{20}-Z- \\ X-N \\ H \end{array}$$;

(h)

$$\begin{array}{c} X \quad X \\ X \quad X \quad Z-R_{20}-Z- \\ X \quad N \\ H \end{array}$$;

(i)

$$\begin{array}{c} (CH_2)d \\ (CH_2)e \quad X_2 \\ X \quad X_5 \quad (CH_2)d \\ X \quad N \\ H \quad Z \quad (CH_2)a \\ O \end{array}$$;

(j)

$$\begin{array}{c} (X_4)_a-(CH_2)a \\ \quad X \quad R_6 \\ C \quad N \quad -C- \\ (CH_2)a \quad N \quad H \quad O \\ H \quad O \end{array}$$;

(k)

$$\begin{array}{c} X_4 \\ C \quad (CH_2)d \\ \quad R_5 \quad R_6 \\ (CH_2)a-N \quad N-C-C- \\ H \quad O \quad R_7 \quad O \end{array}$$;

(l)

$$\begin{array}{c} X_4 \\ C \quad (CH_2)d \\ (CH_2)a-N \quad C-R_{20}-Z- \\ H \quad O \end{array}$$;

(m)

$$\begin{array}{c} X_2 \quad (CH_2)d \\ \quad R_5 \quad R_6 \\ (CH_2)c \quad N-C-C- \\ N \quad O \quad R_7 \quad O \\ H \end{array}$$;

(n)

(o)

5

(p)

(q)

10

(r)

(s)

15

(t)

20

(v)

;

(w)

;

(x)

;

(y)

;

R_{20} is selected from the group consisting of:

(aa1)

;

(aa2)

;

(aa3)

;

(aa4)

;

(aa5)

;

5

(bb)

;

(cc)

;

10   (dd)

;

(ee)

;

15

(ff)

;

(gg)

;

20

(gga)

;

(ggb)

; and

(ggc)

;

wherein each ring C is independently chosen from the group consisting of benzo, pyrido, thieno, pyrrolo, furano, thiazolo, isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo, cyclopentyl, and cyclohexyl;

R_3 is

-CN,

-CH=CH-R_9,

-CH=N-O-R_9,

-$(CH_2)_{1-3}$-T_1-R_9,

-CJ_2-R_9,

-CO-R_{13}, or

$$-CO-CO-N\begin{array}{c}/R_5\\\backslash R_{10}\end{array};$$

each R_4 is independently selected from the group consisting of:

-H,

-Ar_1,

-R_9,

-T_1-R_9, and

$-(CH_2)_{1,2,3}-T_1-R_9$,

each T_1 is independently selected from the group consisting of:

$-CH=CH-$,

$-O-$,

$-S-$,

$-SO-$,

$-SO_2-$,

$-NR_{10}-$,

$-NR_{10}-CO-$,

$-CO-$,

$-O-CO-$,

$-CO-O-$,

$-CO-NR_{10}-$,

$-O-CO-NR_{10}-$,

$-NR_{10}-CO-O-$,

$-NR_{10}-CO-NR_{10}-$,

$-SO_2-NR_{10}-$,

$-NR_{10}-SO_2-$,   and

$-NR_{10}-SO_2-NR_{10}-$,

each R_5 is independently selected from the group consisting of:

$-H$,

$-Ar_1$,

$-CO-Ar_1$,

$-SO_2-Ar_1$,

$-CO-NH_2$,

$-SO_2-NH_2$,

$-R_9$,

$-CO-R_9$,

$-CO-O-R_9$,

$-SO_2-R_9$,

$$-CO-N\diagdown_{R_{10},}^{\diagup Ar_1}$$

5

$$-SO_2-N\diagdown_{R_{10},}^{\diagup Ar_1}$$

$$-CO-N\diagdown_{R_{10},}^{\diagup R_9} \quad \text{and}$$

10

$$-SO_2-N\diagdown_{R_{10},}^{\diagup R_9}$$
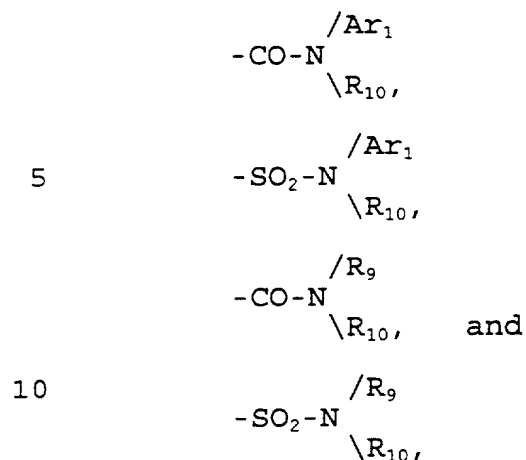
15

R_6 and R_7 taken together form a saturated 4-8 member carbocyclic ring or heterocyclic ring containing -O-, -S-, or -NH-; or

R_7 is -H and R_6 is:

-H,

$-Ar_1$,

$-R_9$,

20

$-(CH_2)_{1,2,3}-T_1-R_9$, or

an α-amino acid side chain residue;

each R_9 is a C_{1-6} straight or branched alkyl group optionally singly or multiply substituted by -OH, -F, or =O and optionally substituted with one or two Ar_1

25

groups;

each R_{10} is independently selected from the group consisting of -H or a C_{1-6} straight or branched alkyl group;

each R_{13} is independently selected from the group

30

consisting of $-Ar_2$, $-R_4$ and $-N-OH$

$$\diagdown_{R_5} \quad ;$$

each Ar_1 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, a cycloalkyl group which contains between 3 and 15 carbon atoms and between 1 and 3 rings, said cycloalkyl group being optionally benzofused, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocycle group containing at least one heteroatom group selected from -O-, -S-, -SO-, -SO$_2$-, =N-, and -NH-, said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -NH$_2$, -CO$_2$H, -Cl, -F, -Br, -I, -NO$_2$, -CN, =O, -OH, -perfluoro C$_{1-3}$ alkyl,

$$\underset{O}{\overset{O}{\diamond}}\!\!CH_2, \quad \text{or } -Q_1;$$

each Ar_2 is independently selected from the following group, in which any ring may optionally be singly or multiply substituted by -Q$_1$ and -Q$_2$:

(hh)

,

(ii)

,

(jj)

, and

(kk)

;

each Q_1 is independently selected from the group consisting of

$-Ar_1$

$-O-Ar_1$

$-R_9$,

$-T_1-R_9$,   and

$-(CH_2)_{1,2,3}-T_1-R_9$;

each Q_2 is independently selected from the group consisting of $-OH$, $-NH_2$, $-CO_2H$, $-Cl$, $-F$, $-Br$, $-I$, $-NO_2$, $-CN$, $-CF_3$, and

$$\underset{O}{\overset{O}{\triangle}}CH_2;$$

provided that when $-Ar_1$ is substituted with a Q_1 group which comprises one or more additional $-Ar_1$ groups, said additional $-Ar_1$ groups are not substituted with Q_1;

each X is independently selected from the group consisting of $=N-$, and $=CH-$;

each X_2 is independently selected from the group consisting of $-O-$, $-CH_2-$, $-NH-$, $-S-$, $-SO-$, and $-SO_2-$;

each X_3 is independently selected from the group consisting of $-CH_2-$, $-S-$, $-SO-$, and $-SO_2-$;

each X_4 is independently selected from the group consisting of $-CH_2-$ and $-NH-$;

each X_5 is independently selected from the group consisting of $-\overset{|}{C}H-$ and $-\overset{|}{N}-$;

X_6 is CH or N, provided that when X_6 is N in the R_1 group labeled (o) and X_5 is CH and X_2 is CH_2 the ring of the R_1 group labeled (o) must be substituted by Q_1 or benzofused;

each Y is independently selected from the group consisting of -O- and -S-, and -NH;

each Z is independently CO or SO_2,

each a is independently 0 or 1,

each c is independently 1 or 2,

each d is independently 0, 1, or 2, and

each e is independently 0, 1, 2, or 3,

provided that when
    R_1 is (f),
    R_6 is an α-amino acid side chain residue, and
    R_7 is -H,
then (aa1) and (aa2) must be substituted with Q_1;

also provided that when
    R_1 is (o),
    g is 0,
    J is -H,
    m is 1,
    R_6 is an α-amino acid side chain residue,
    R_7 is -H,
    X_2 is $-CH_2-$,
    X_5 is $-\overset{|}{C}H-$,

    X_6 is $-\overset{|}{N}-$, and

R_3 is

$$-CO-N\begin{array}{c}/R_{10}\\\backslash R_{10}\end{array}, \text{ or } -CO-R_{13}, \text{ when}$$

R_{13} is:

-CH_2-O-CO-Ar_1,

-CH_2-S-CO-Ar_1,

-CH_2-O-Ar_1,

-CH_2-S-Ar_1, or

-R_4 when -R_4 is -H;
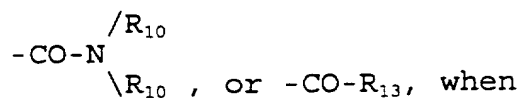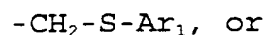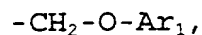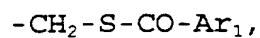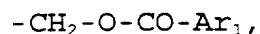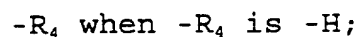
then the ring of the R_1(o) group must be substituted with Q_1 or benzofused; and

provided that when

R_1 is (w),

g is 0,

J is -H,

m is 1,

T is -CO_2H or -CO-NH-OH,

X_2 is O,

R_5 is benzyloxycarbonyl, and

ring C is benzo,

then R_3 cannot be -CO-R_{13} when:

R_{13} is -CH_2-O-Ar_1 and

Ar_1 is 1-phenyl-3-chloro- or

3-trifluoromethyl-pyrazole-5-yl;

or when

R_{13} is -CH_2-O-CO-Ar_1 and

Ar_1 is 2,6-dichlorophenyl.

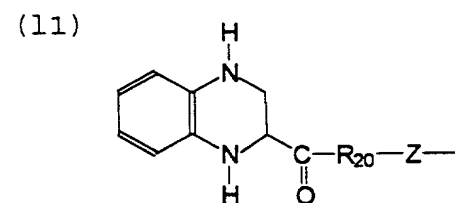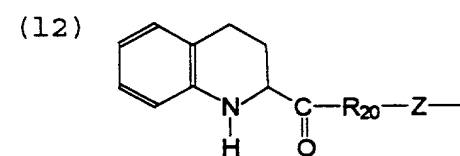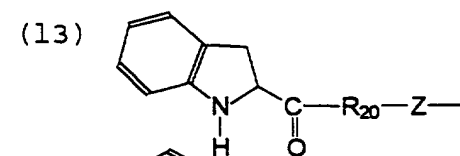Preferred forms of the R_1 group (a) for embodiments A and B are:

(a1)

; and

(a2)

.
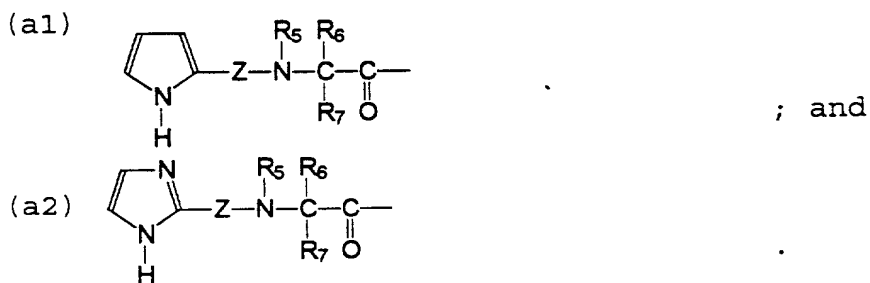
Preferred forms of the R_1 group (b) are:
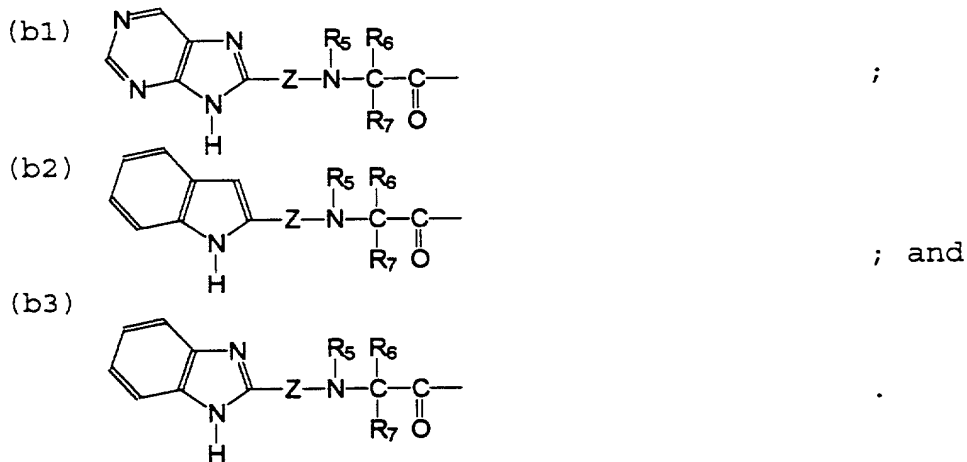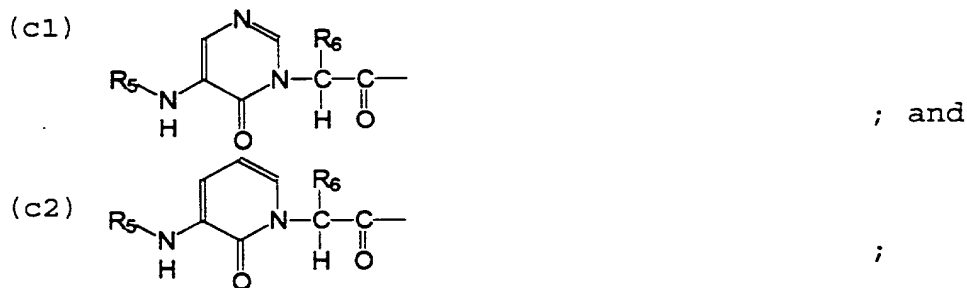
(b1)

;

(b2)

; and

(b3)

.

Preferred forms of the R_1 group (c) are:

(c1)

; and

(c2)

;

provided that when R_1 is (c1),

      g is 0,

      J is -H,

      m is 1,

      T is $-CO_2H$,

      X is N,

      R_5 is benzyloxycarbonyl, and

      R_6 is -H,

then R$_3$ cannot be -CO-R$_{13}$ when

    R$_{13}$ is -CH$_2$-O-Ar$_1$ and

    Ar$_1$ is a chloro-substituted 1-phenyl-3-trifluoromethyl-pyrazole-5-yl, or when

    R$_{13}$ is -CH$_2$-O-CO-Ar$_1$ and

    Ar$_1$ is 2,6-dichlorophenyl,

and when the 2-position of the scaffold ring is substituted with para-fluoro-phenyl;

Preferred forms of the R$_1$ group (d) are:

(d1)

           ;

(d2)

           ;

(d3)

           ; and

(d4)
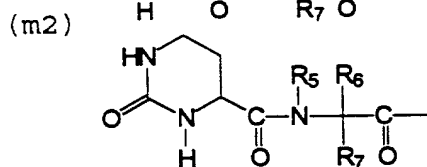
           .

Preferred forms of the R$_1$ group (e) are:

(e1)

           ;

(e2)

$$R_5-NH-\ldots(CH_2)_c\ldots N-(CH_2)_c\ldots$$

;

(e3)

;

(e4)

;

(e5)

;

(e6)

;

(e7)

which is optionally benzofused;

(e8)

; and

(e9)

;

provided that when R_1 is (e4),

    g is 0,

    J is -H,

    m is 1,

    T is $-CO_2H$,

    R_5 is benzyloxycarbonyl, and

    c is 1,

then R_3 cannot be $-CO-R_{13}$ when

    R_{13} is $-CH_2-O-Ar_1$ and

    Ar_1 is 1-phenyl-3-trifluoromethyl-pyrazole-

5-yl, wherein the phenyl is optionally substituted with

a chlorine atom; or when

    R_{13} is $-CH_2-O-CO-Ar_1$ and

    Ar_1 is 2,6-dichlorophenyl,

    and when the 2-position of the scaffold ring is

substituted with para-fluoro-phenyl; and

    also provided that when

    R_1 is (e7),

    g is 0,

    J is -H,

    m is 1,

    T is $-CO_2H$ or $-CO-NH-OH$,

    R_5 is a protective group for the N atom of an

amino acid side chain residue, and

    each c is 1,

    then R_3 cannot be $-CO-R_{13}$ when

    R_{13} is:

$-CH_2-O-CO-Ar_1,$

$-CH_2-S-CO-Ar_1,$

$-CH_2-O-Ar_1,$ or

$-CH_2-S-Ar_1.$

Preferred forms of the R_1 group (g) are:

(g1)

; and

(g2)

.

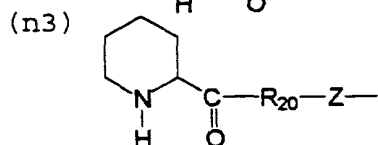Preferred forms of the R_1 group (h) are:

(h1)

;

(h2)

; and

(h3)

.

Preferred forms of the R_1 group (i) are:

(i1)

;

(i2)

;

(i3)

; and

(i4)

.

5

Preferred forms of the R_1 group (j) are:

(j1)

;

10

(j2)

;

(j3)

; and

15

(j4)

Preferred forms of the R_1 group (k) are:

20   (k1)

;

- 55 -

(k2)

;

(k3)

;

(k4)

; and

(k5)

.

Preferred forms of the R₁ group (l) are:

(l1)

;

(l2)

;

(l3)

;

(l4)

; and

(15)
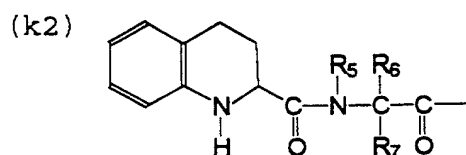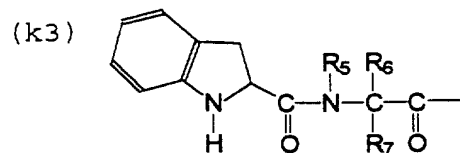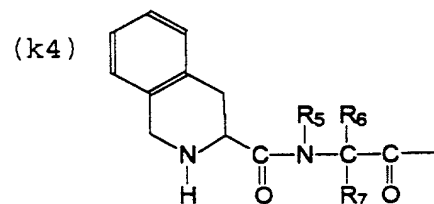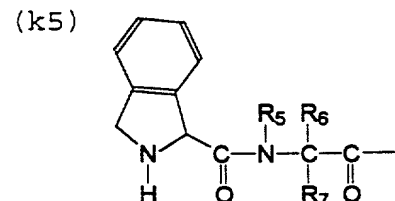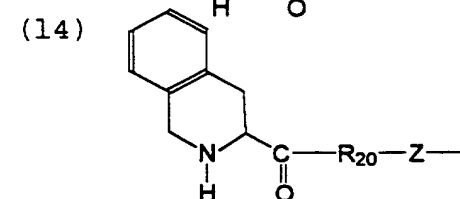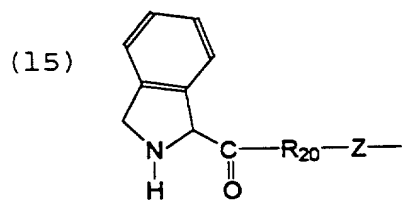
Preferred forms of the R₁ group (m) are:

(m1)

;

(m2)

;

(m3)

;

(m4)

;

(m5)

; and

(m6)

.

Preferred forms of the R₁ group (n) are:

(n1)

;

(n2)

R_{20}—Z—

;

(n3)

R_{20}—Z—

;

5 (n4)

R_{20}—Z—

;

(n5)

R_{20}—Z—

; and

10 (n6)

R_{20}—Z—

.

Preferred forms of the R_1 group (o) are:

(o1)

$(CH_2)d$ R_9 R_6

R_5—N

;

15 (o2)

$(O)d$

R_6

R_5—N

;

(o3)
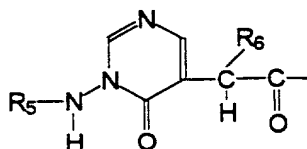
$(O)d$

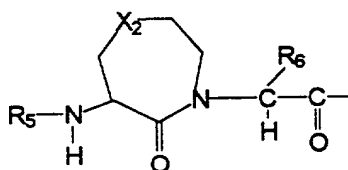R_6

R_5—N

;

(o4)

$(CH_2)d$ R_6

R_5—N

; and

20
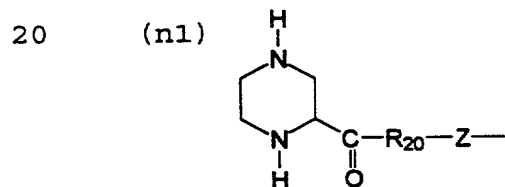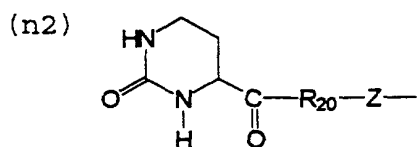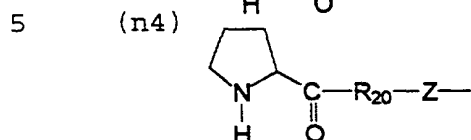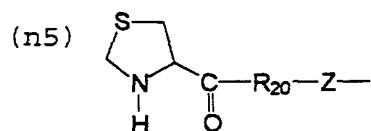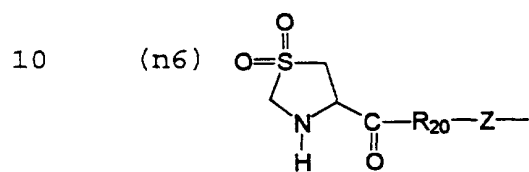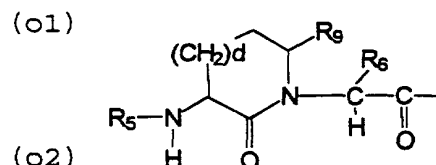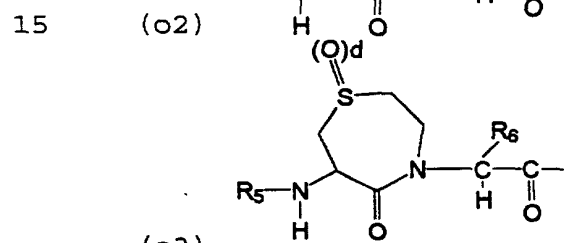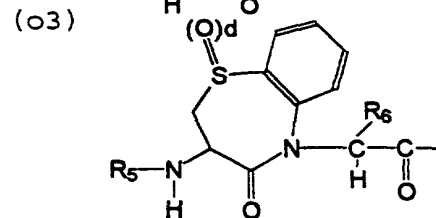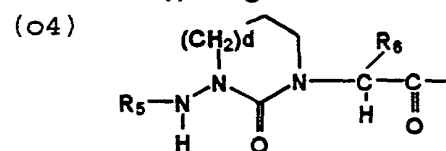
(o5)

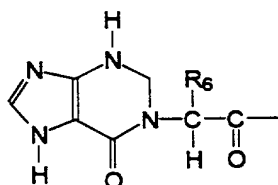A preferred form of the R_1 group (o) of embodiment B is:

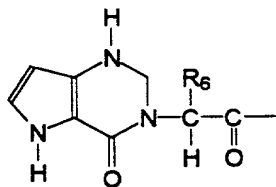(o6)

wherein X_2 is -O-, -S-, -SO$_2$-, or -NH-.

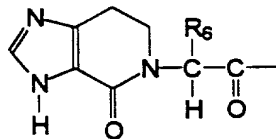For embodiments A and B, preferred forms of the R_1 group (p) are:

(p1)

;

(p2)

;

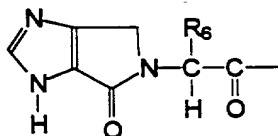(p3)
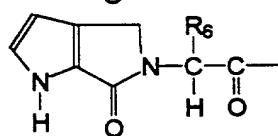

;

(p4)

; and

(p5)

.

Preferred forms of the R$_1$ group (q) are:

(q1)

;

(q2)

5

;

(q3)

;

(q4)

10

;

(q5)

; and

(q6)

.
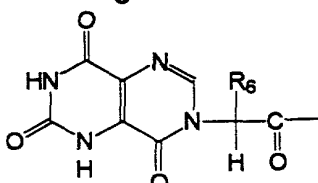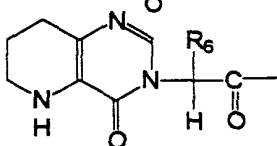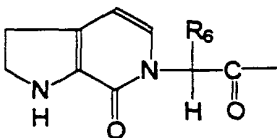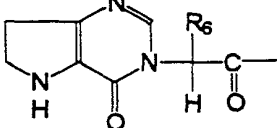
15   Preferred forms of the R$_1$ group (r) are:

(r1)

;

(r2)

;

20   (r3)

;

(r4)
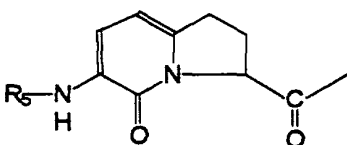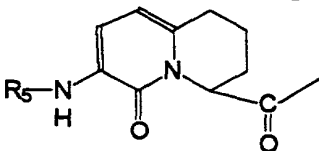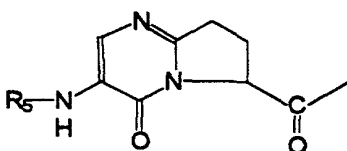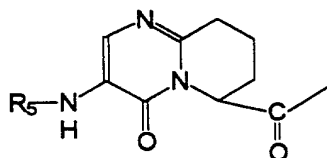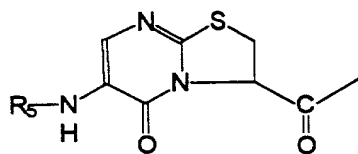
(r5)
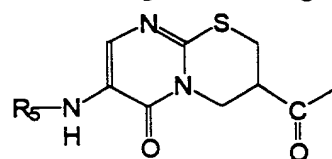
(r6) ; and

(r7)
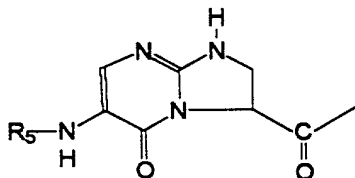
Preferred forms of the R_1 group (s) are:

(s1) ;

(s2) ;
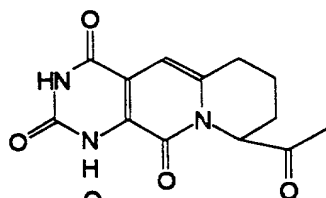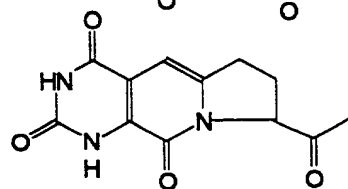
(s3) ; and
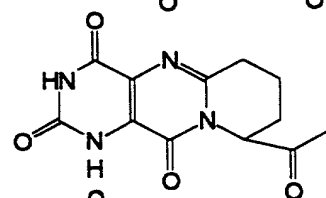
(s4)
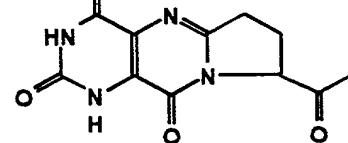
Preferred forms of the R$_1$ group (t) are:
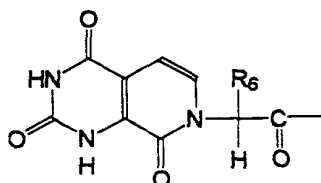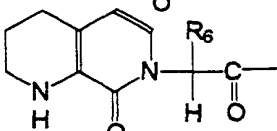
(t1)

;

(t2)

;

(t3)

;

(t4)

; and

(t5)

.
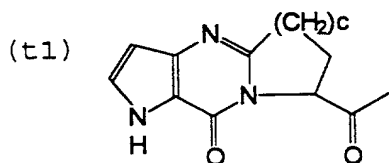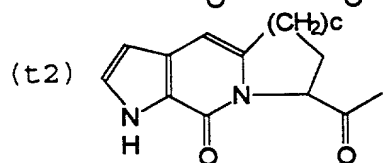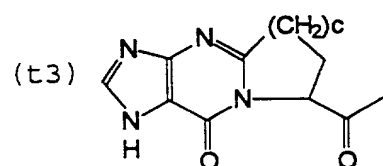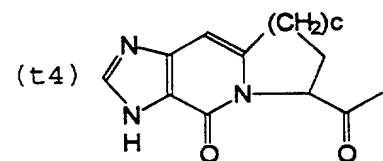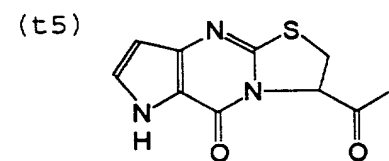
Preferred forms of the R$_1$ group (v) are:

(v1)

;

(v2)

;

(v3)

; and

(v4)

.
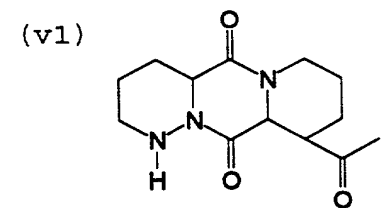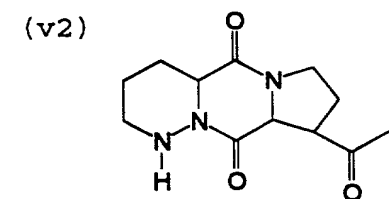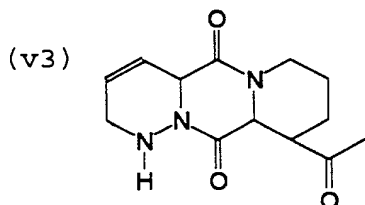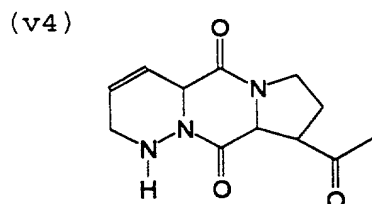
A preferred form of the R1 group (w) of embodiment B is:

(w1)

,
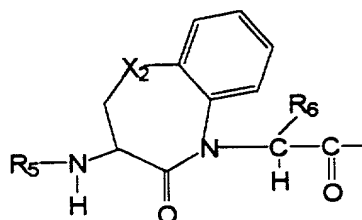
wherein X_2 is -O-, -S-, -SO$_2$- or -NH-.

The preferred compounds of embodiments A and B of this invention are those which employ formula α, wherein:

X_1 is CH;

g is O;

J is -H;

m is 0 or 1 and T is -Ar$_3$, -CO-CO$_2$H, -CO$_2$H or any bioisosteric replacement for -CO$_2$H, or

m is 1 or 2 and T is -OH, -CF$_3$, or -CO$_2$H;

more preferably m is 1 and T is -CO$_2$H;

R₁ is

(c)

,

(d)

,

(e)

,

(f)

,

(g)

, or

(r)

;

R₂₀ is

(aa1)

,
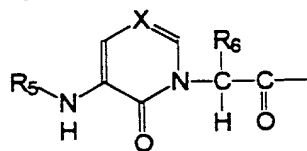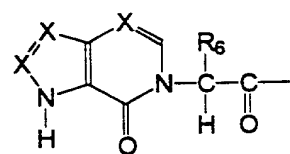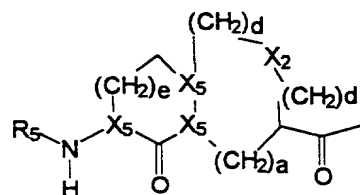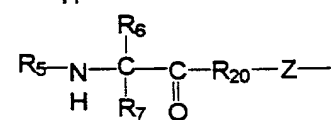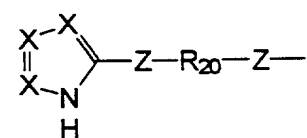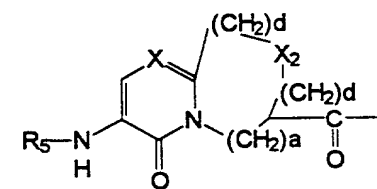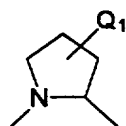
(aa2)

,
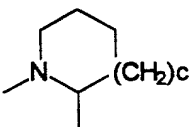
(aa3)
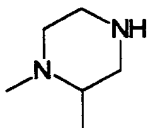
, or

(dd)
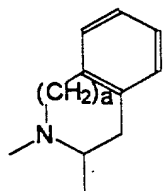
wherein ring C is benzo;

R_3 is

$-CO-R_{13}$, or

$$-CO-CO-N\begin{array}{c} /R_5 \\ \backslash R_{10} \end{array};$$

most preferably R_3 is any one of 1), 2) or 3) as follows: 1) $-CO-Ar_2$, 2) $-CO-R_9$ where R_9 is C_{3-6} alkyl substituted with two Ar_1 groups or one Ar_1 group itself substituted with an Ar_1 group, $-C_{1-2}-Ar_1$, $-Cl$, $-CH_3$, or $-CF_3$, or 3) $-(CH_2)_{1,2}-T_1-R_9$ where T_1 is $-O-$ or $-S-$ and R_9 is C_{1-2} alkyl substituted with two Ar_1 groups or one Ar_1 group itself substituted with an Ar_1 group, $C_{1-2}-Ar_1$, $-Cl$, $-CH_3$, or $-CF_3$;

R_4 is $-H$ or $-R_9$;

T_1 is

$-O-$,

$-S-$,

$-CO-$,

$-O-CO-$, or

$-SO_2-$;

when R_1 is (a), (b), (k), or (m), R_5 is preferably $-Ar_1$ or $C_{1-4}-Ar_1$;

when R_1 is (c), (e), (f), (o), or (r), R_5 is preferably $-SO_2-Ar_1$, $-SO_2-R_9$, or $-CO-C_{1-4}-Ar_1$;

R_7 is $-H$ and R_6 is $C_{1-4}-Ar_1$;

R_{10} is $-H$ or a C_{1-3} straight or branched alkyl group;

R_{13} is $-Ar_2$;

Ar_1 is phenyl, naphthyl, pyridyl, benzothiazolyl, thienyl, benzothienyl, benzoxazolyl, 2-indanyl, or indolyl;

Ar_2 is preferably substituted with $-Ar_1$, or $-C_{1-4}-Ar_1$;

Ar_3 is phenyl, thiophene, thiazole, pyridine, or oxazole; and

Q_1 is $-R_9$ or $-(CH_2)_{1,2}-T_1-(CH_2)_{1-3}-Ar_1$ where T_1 is $-O-$ or $-S-$.

In connection with this continuation-in-part, we now prefer the compounds of embodiment B of this invention which employ formula α, wherein:

X_1 is $-CH$;

g is O;

J is $-H$;

m is 0 or 1 and T is $-CO-CO_2H$, or any bioisosteric replacement for $-CO_2H$; or

m is 1 and T is $-CO_2H$;

R$_1$ is selected from the group consisting of the following formulae, in which any ring may optionally be singly or multiply substituted at any carbon by Q_1, at any nitrogen by R_5, or at any atom by $=O$, $-OH$, $-CO_2H$, or halogen, and wherein (e) is optionally benzofused:

(a)

$$X-X$$
$$X \diagdown \diagup$$
$$N$$
$$H$$
$$-Z-N(R_5)-C(R_6)(R_7)-C(=O)-$$

,

(b)

fused bicyclic ring system $-Z-N(R_5)-C(R_6)(R_7)-C(=O)-$

,

(c)

R_5-NH- pyridinone ring $-N-C(R_6)(H)-C(=O)-$

,

(e)

R_5-NH- ... $(CH_2)e$ X_5 ... X_6 ... X_5 ... $(CH_2)d$ X_2 $(CH_2)d$ $(CH_2)a$ ...

,

(f)

$R_5-N(H)-C(R_6)(R_7)-C(=O)-R_{20}-Z-$

,

(g)

$$X-X$$
$$X \diagdown \diagup$$
$$X-N$$
$$H$$
$$-Z-R_{20}-Z-$$

,

(h)

fused bicyclic ring system $-Z-R_{20}-Z-$

,

(o)

R_5-NH- ... X_5 $(CH_2)c$ X_2 H $(CH_2)d$ X_6 $-C(R_6)(H)-C(=O)-$

,

(r)

R₅-NH... (CH₂)d, X, X₂, (CH₂)d, (CH₂)a, C, O ...structure..., or

(w)

X₂, C, R₆, R₅-NH, N, C, C, O ...structure... ;

R_{20} is

(aa1) ...pyrrolidine structure..., or

(aa2) ...piperidine structure with $(CH_2)c$...
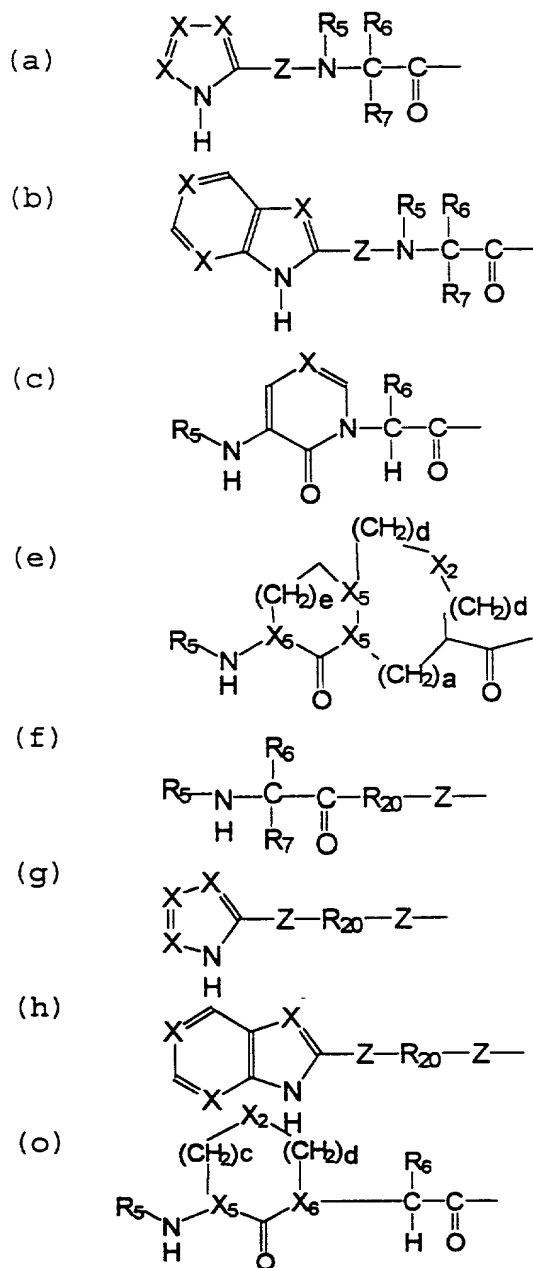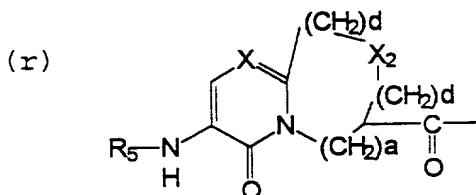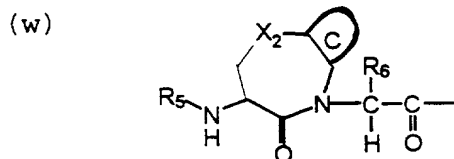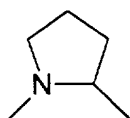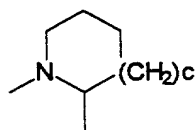
and c is 1;

ring C is benzo optionally substituted with $-C_{1-3}$ alkyl, $-O-C_{1-3}$ alkyl, $-Cl$, $-F$ or $-CF_3$;

R_3 is:

    $-CO-R_{13}$, or

$$-CO-CO-N\begin{array}{l} /R_9 \\ \backslash R_{10} \end{array};$$

more preferably R_3 is any one of 1), 2) or 3) as follows: 1) $-CO-Ar_2$; 2) $-CO-R_9$ where R_9 is C_{1-5} alkyl substituted with an Ar_1; or 3) $-CH_2-T_1-R_9$ where T_1 is $-O-$ or $-S-$ and R_9 is C_{1-2} alkyl substituted with one Ar_1 group;

R_4 is $-H$ or $-R_9$;

T_1 is:

-O-,

-S-,

-CO-,

-O-CO-, or

-SO_2-;

when R_1 is (a) or (b), R_5 is preferably -H, and when R_1 is (c), (e), (f), (o), (r), (w), (x) or (y), R_5 is preferably:

-CO-Ar_1

-SO_2-Ar_1,

-CO-NH_2,

-CO-NH-Ar_1

-CO-R_9,

-CO-O-R_9,

-SO_2-R_9, or

-CO-NH-R_9,

.

R_7 is -H and R_6 is

-H,

-R_9 or

-Ar_1;

R_9 is C_{1-6} straight or branched alkyl group optionally substituted with =O and optionally substituted with -Ar_1;

R_{10} is -H or a C_{1-3} straight or branched alkyl group;

R_{13} is:

-H,

-R_9,

-Ar_2, or

$-CH_2-T_1-R_9,$
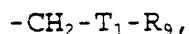
more preferably where $-Ar_2$ is
(hh) and where (hh) is optionally substituted singly or
multiply with $-C_{1-6}$ alkyl, $-O-C_{1-6}$ alkyl,
$-NH-C_{1-6}$ alkyl, $-N-(C_{1-6}$ alkyl$)_2$, $-S-C_{1-6}$ alkyl, $-Cl$,
$-F$, $-CF_3$, or

$$\begin{array}{c} O \\ / \backslash \\ CH_2 \ ; \\ \backslash / \\ O \end{array}$$

Ar_1 is phenyl, naphthyl, pyridyl, benzothiazolyl,
thienyl, benzothienyl, benzoxazolyl, 2-indanyl, or
indolyl substituted with $-O-C_{1-3}$ alkyl, $-NH-C_{1-3}$ alkyl, -
$N-(C_{1-3}$ alkyl$)_2$, $-Cl$, $-F$, $-CF_3$,
$-C_{1-3}$ alkyl, or

$$\begin{array}{c} O \\ / \backslash \\ CH_2 \ ; \\ \backslash / \\ O \end{array}$$
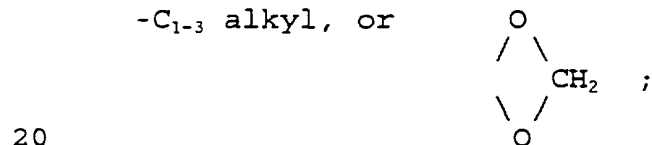
preferably where Ar_2 is:

(ii)

,

(jj)
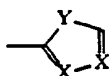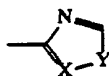
, or

(kk)

,

each X is independently selected from the group
consisting of $=N-$, and $=CH-$;

each X_2 is independently selected from the group
consisting of $-O-$, $-CH_2-$, $-NH-$, $-S-$, $-SO-$, and $-SO_2-$;

each X_5 is independently selected from the group
consisting of $-\overset{|}{CH}-$ and $-\overset{|}{N}-$;

X_6 is $-\overset{|}{CH}-$ or $-\overset{|}{N}-$; and

Z is $C=O$;

provided that when
    R_1 is (f),
    R_6 is an α-amino acid side chain residue, and
    R_7 is $-H$,
then (aa1) and (aa2) must be substituted with Q_1;

also provided that when
    R_1 is (o),
    g is 0,
    J is $-H$,
    m is 1,
    R_6 is an α-amino acid side chain residue,
    R_7 is $-H$,
    X_2 is $-CH_2-$,
    X_5 is $-\overset{|}{CH}-$,

    X_6 is $-\overset{|}{N}-$, and

    R_3 is
$$-CO-N\begin{matrix} /R_{10} \\ \backslash R_{10} \end{matrix} \text{ , or}$$
      $-CO-R_{13}$, when

R_{13} is:

-CH_2-O-CO-Ar_1,

-CH_2-S-CO-Ar_1,

-CH_2-O-Ar_1,

-CH_2-S-Ar_1, or

-R_4 when -R_4 is -H;

then the ring of the R_1(o) group must be substituted with Q_1 or benzofused; and

provided that when

R_1 is (w),

g is 0,

J is -H,

m is 1,

T is -CO_2H,

X_2 is O,

R_5 is benzyloxycarbonyl, and

ring C is benzo,

then R_3 cannot be -CO-R_{13} when:

R_{13} is -CH_2-O-Ar_1 and

Ar_1 is 1-phenyl-3-trifluoromethyl-pyrazole-5-yl, wherein the phenyl is optionally substituted with a chlorine atom;

or when R_{13} is -CH_2-O-CO-Ar_1, wherein Ar_1 is 2,6-dichlorophenyl.

A preferred form of R_{13} is -CH_2-O-R_9, wherein R_9 is a C_{1-6} straight or branched alkyl group optionally substituted with =O and optionally substituted with Ar_1;

another preferred form of R_{13} is CH_2-S-R_9, wherein R_9 is a C_{1-6} straight or branched alkyl group optionally substituted with Ar_1;

another preferred form of R_{13} is CH_2-O-R_9 wherein R_9 is a C_{1-6} straight or branched alkyl group optionally substituted with Ar_1;

another preferred form of R_{13} is H.

A more preferred form of the R_1 group (a) is:
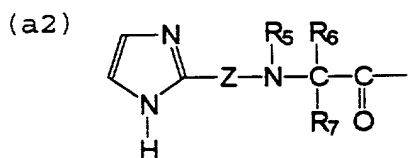
(a2)

optionally substituted with Q_1, wherein

R_5 is -H;

R_7 is -H; and

Z is $C=O$;

a more preferred form of the R_1 group (b) is:

(b)

optionally substituted with Q_1, wherein

R_5 is -H;

R_7 is -H; and

Z is $C=O$;

more preferred forms of the R_1 group (c) are:
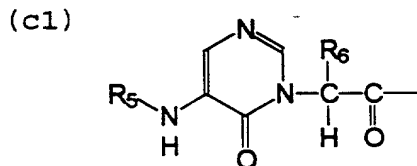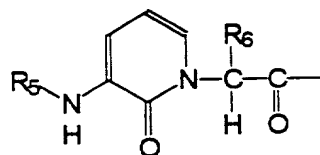
(c1)

, and

(c2)

provided that when R_1 is (c1),

g is 0,

J is -H,

m is 1,

T is -CO_2H,

X is N,

R_5 is benzyloxycarbonyl, and

R_6 is -H,

then R_3 cannot be -CO-R_{13} when

R_{13} is -CH_2-O-Ar_1 and

Ar_1 is 1-phenyl-3-trifluoromethyl-pyrazole-5-yl wherein the phenyl is optionally substituted with a chlorine atom; or when

R_{13} is -CH_2-O-CO-Ar_1, wherein

Ar_1 is 2,6-dichlorophenyl,

and wherein the 2-position of the scaffold ring is substituted with para-fluoro-phenyl;

more preferred forms of the R_1 group (e) are:

(e1)
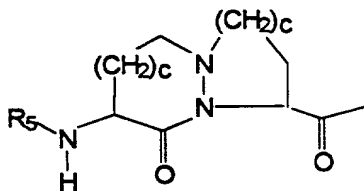
, and

(e2)

,
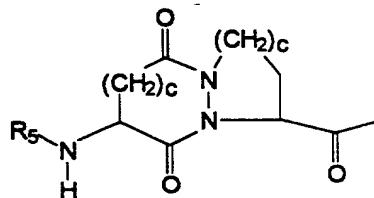
wherein c is 2; and

(e4)
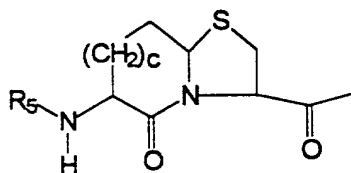
, and

(e7)
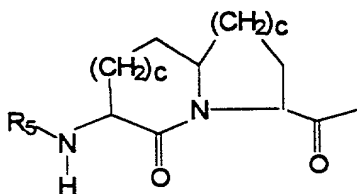
which is optionally
benzofused,

wherein c is 1 or 2;

provided that when R_1 is (e4),

        g is 0,

        J is -H,

        m is 1,

        T is $-CO_2H$,

        R_5 is benzyloxycarbonyl, and

        c is 1,

then R_3 cannot be $-CO-R_{13}$ when

        R_{13} is $-CH_2-O-Ar_1$ and

        Ar_1 is 1-phenyl-3-trifluoromethyl-pyrazole-

5-yl wherein the phenyl is optionally substituted with
a chlorine atom; or when

        R_{13} is $-CH_2-O-CO-Ar_1$, wherein

        Ar_1 is 2,6-dichlorophenyl,

and wherein the 2-position of the scaffold ring is
substituted with para-fluoro-phenyl; and

also provided that when

        R_1 is (e7),

        g is 0,

        J is -H,

        m is 1,

T is $-CO_2H$, $-CO-NH-OH$, or a bioisosteric replacement for $-CO_2H$,

R_5 is a protective group for the N atom of an α-amino acid side chain residue, and

each c is 1,

then R_3 cannot be $-CO-R_{13}$ when R_{13} is:

$-CH_2-O-CO-Ar_1$,

$-CH_2-S-CO-Ar_1$,

$-CH_2-O-Ar_1$, or

$-CH_2-S-Ar_1$.

a more preferred form of the R_1 group (f) is

(f1)

;
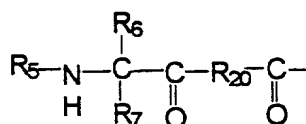
a more preferred form of the R_1 group (g) is:

(g2)
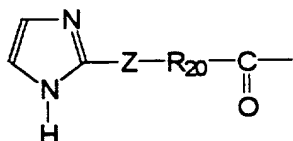
; wherein

R_{20} is (aa1) optionally substituted singly or multiply with Q_1; and

Z is C=O;

a more preferred form of the R_1 group (h) is:

(h)
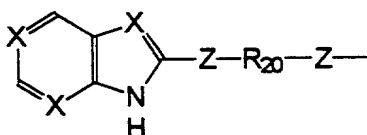
; wherein

R_{20} is (aa1) optionally substituted singly or multiply with Q_1; and

Z is C=O;

more preferred forms of the R_1 group (o) are:

5   (o1)

;
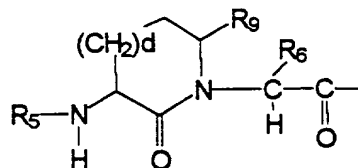
wherein d is 1 or 2; and

(o6)

;
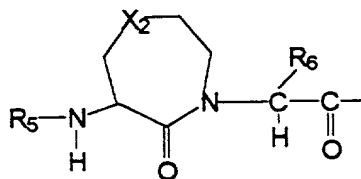
10   more preferred forms of the R_1 group (r) are:

(r3)

;
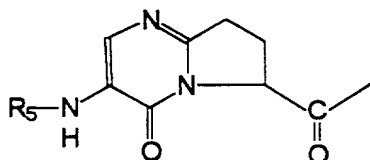
(r4)
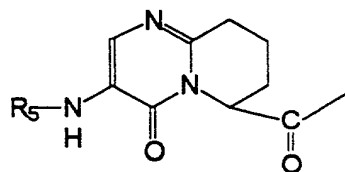
; and

15   (r5)
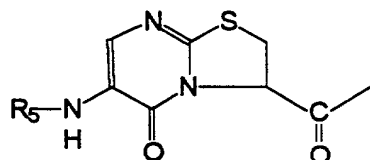
optionally substituted with Q_1;

a more preferred form of the R_1 group (w) is:

(w1)

; wherein

X_2 is:

 -NH-,

 -S- ,

 -O- , or

 -SO_2- ;
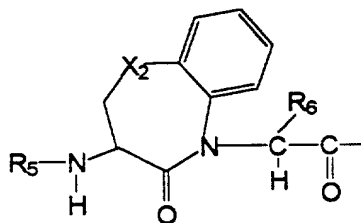
optionally substituted with R_5 or Q_1 at X_2
when X_2 is -N-; and

ring C is benzo substituted with -C_{1-3} alkyl,
-O-C_{1-3} alkyl, -Cl, -F or -CF_3.

When R_1 is:

(a2)
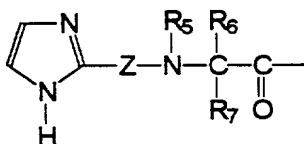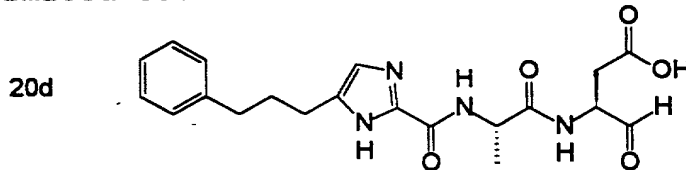
preferred compounds of this invention include but are
not limited to:

20d

; and

142
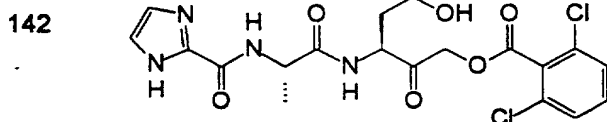
A preferred compound of embodiment B of this invention employs formula α, wherein the R_1 is:

(c2)

5   Preferred compounds of this embodiment include but are not limited to:

54a

;

10   54b

;

54g

;

54j

15

;

54k

;

20   57b

;

88 ;

90 ;

91 ;

125a ;

126 ;

127 ;

128

5

129

10

130

; and

15

131

When R_1 is:

(e)

preferred compounds of this invention include but are
not limited to:

132a

;

132b

133

140

141

; and

.

A preferred compound of embodiment B of this invention employs formula α, wherein:

R_1 is:

(e1)

, or

(e2)

,

and c is 2;

m is 1;
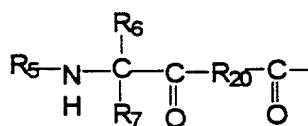
T is -CO$_2$H; and

R$_3$ is -CO-R$_{13}$.

Preferred compounds of this embodiment include but are not limited to:

5

47a

;

47b

;

10

125b

;

15

135a

;

135b

;

20

136

;

137

;

5

138

; and

10

139

.

When R_1 is:

15   (f1)

,

preferred compounds of this invention include but are not limited to:

20

86

;

87

;

158

; and

160

.
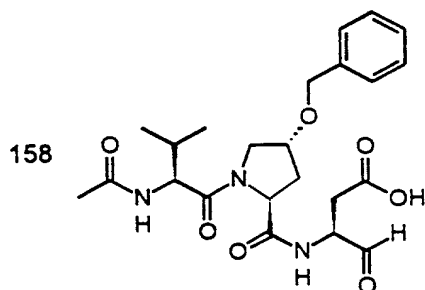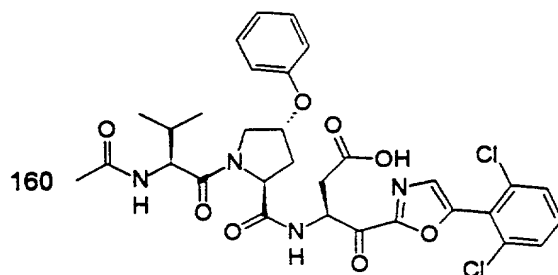
When R$_1$ is:

(g2)

preferred compounds of this invention include but are not limited to:

21d

;

21e

;

21f

;

22e

; and

157

.
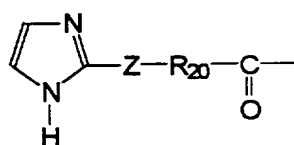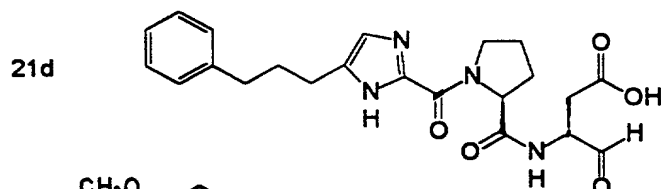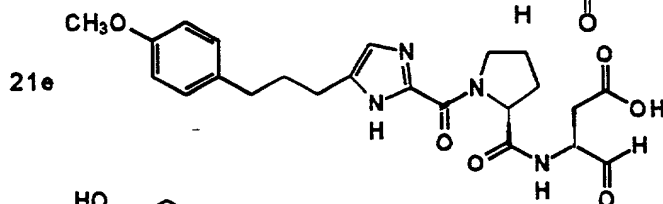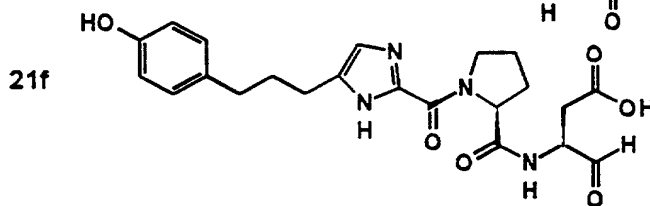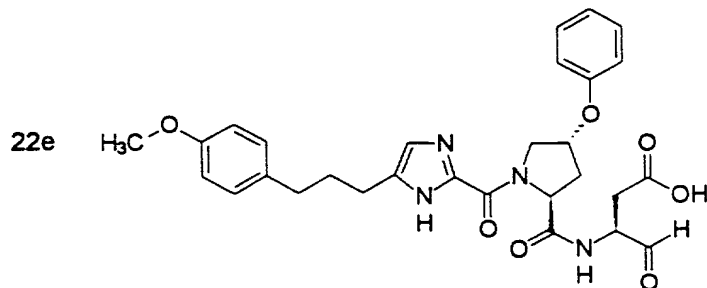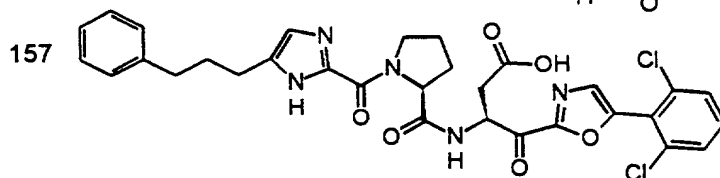
When R_1 is:

(o)

,

preferred compounds of this invention include but are not limited to:

92

.
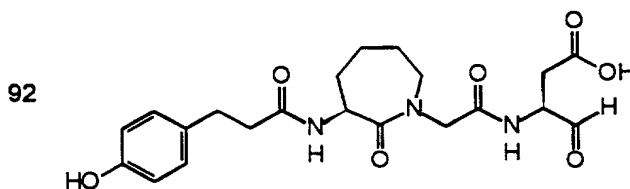
A preferred compound of embodiment B of this invention employs formula α, wherein:

R_1 is:

(o6)

;
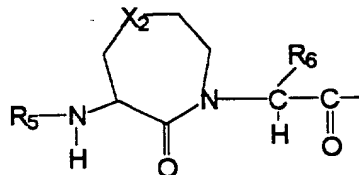
X_2 is -NH-;

m is 1;

T is -CO$_2$H;

R$_3$ is -CO-R$_{13}$.

Preferred compounds of this embodiment include but are not limited to:
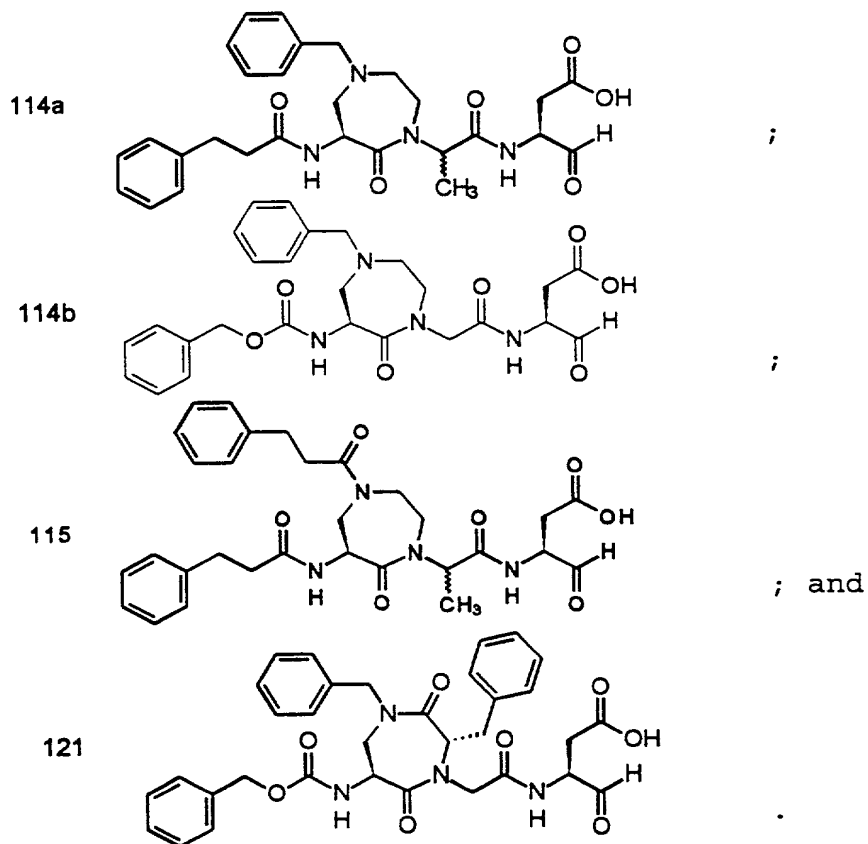
114a

;

114b

;

115

; and

121

.

When R$_1$ is:

(r3)

;

(r4)

; or

(r5)

5   optionally substituted with Q_1;

preferred compounds of embodiment B of this invention include but are not limited to:

98

;

102a

;

102b

; and

102c

.

15

When R₁ is:

(w1)

;
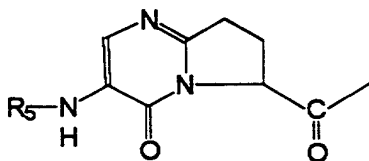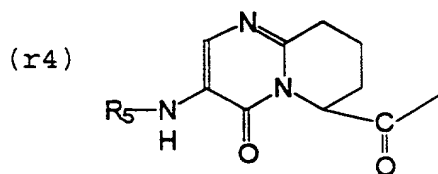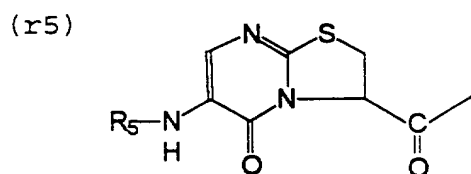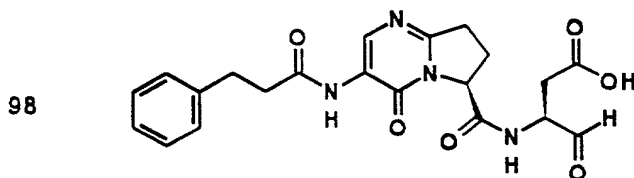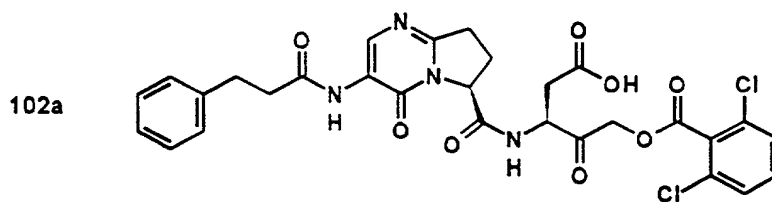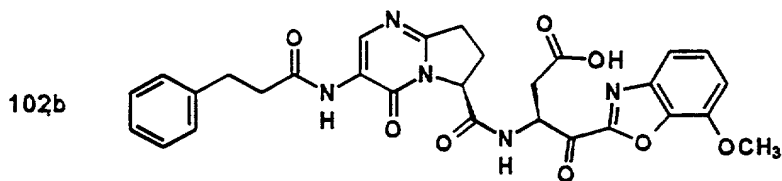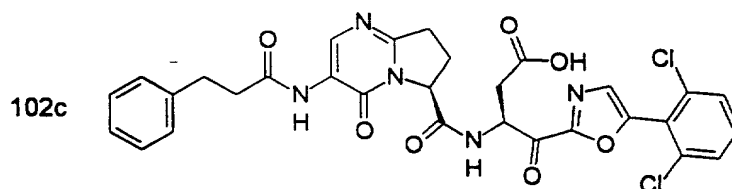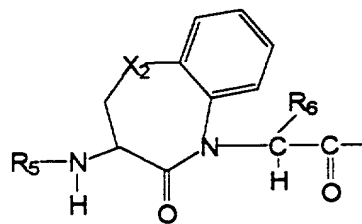
preferred compounds of this invention include but are not limited to:

106a

;
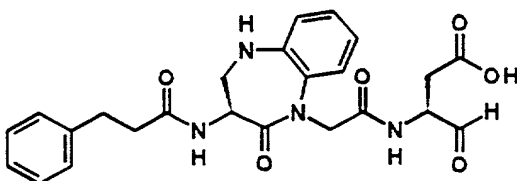
106b

;

106c

;

108a

;

108b

; and

108c
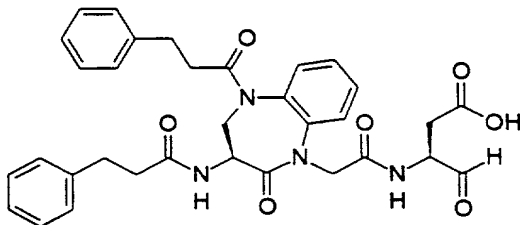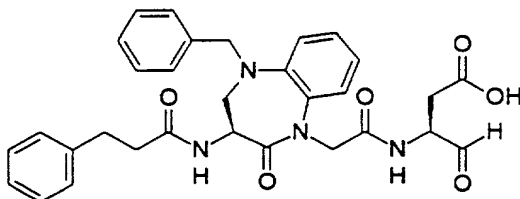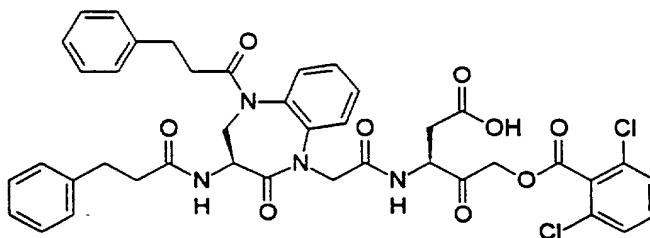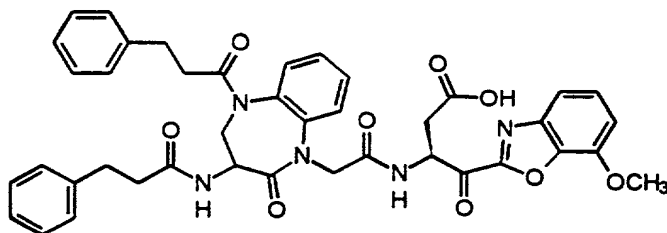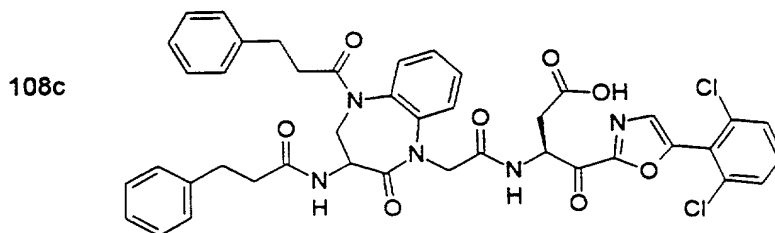
The ICE inhibitors of another embodiment (C) of this invention are represented by the formula $\underline{C}$:

$\underline{C}$
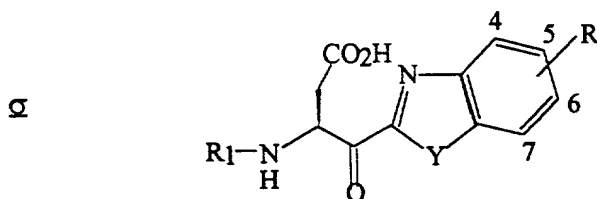
wherein the ring is optionally substituted with one or more R groups, preferably 0, 1 or 2; and wherein:

R_1 is $R_5-(A)_p-$;

R_5 is selected from the group consisting of:
-H,
-Ar_1,
-CO-Ar_1,
-SO_2-Ar_1,
-R_9,
-CO-R_9,
-CO-O-R_9,
-SO_2-R_9,
-CO-N$\begin{array}{l}/Ar_1\\\backslash R_{10}\end{array}$,

$$-SO_2-N\begin{array}{c}/Ar_1 \\ \backslash R_{10},\end{array}$$

$$-CO-N\begin{array}{c}/R_9 \\ \backslash R_{10},\end{array} \quad \text{and}$$

$$-SO_2-N\begin{array}{c}/R_9 \\ \backslash R_{10};\end{array}$$
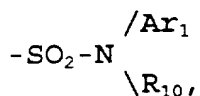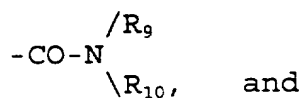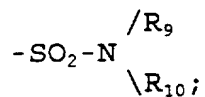
each A is independently selected from the group consisiting of any α-amino acid;

p is 0, 1, 2, 3 or 4;

Y is:
-O-,
-S- or
-NH;

R is:
-H,
-O-C_{1-6} alkyl,
-NH(C_{1-6} alkyl),
-N(C_{1-6} alkyl)$_2$,
-S-C_{1-6} alkyl,
-C_{1-6} alkyl, or
-Q_2;

each R_9 is a C_{1-6} straight or branched alkyl group optionally singly or multiply substituted by -OH, -F, or =O and optionally substituted with one or two Ar_1 groups;

each R_{10} is independently selected from the group consisting of -H or a C_{1-6} straight or branched alkyl group;

each T_1 is independently selected from the group consisting of:

-CH=CH-,

-O-,

-S-,

-SO-,

-SO_2-,

-NR_{10}-,

-NR_{10}-CO-,

-CO-,

-O-CO-,

-CO-O-,

-CO-NR_{10}-,

-O-CO-NR_{10}-,

-NR_{10}-CO-O-,

-NR_{10}-CO-NR_{10}-,

-SO_2-NR_{10}-,

-NR_{10}-SO_2-,   and

-NR_{10}-SO_2-NR_{10}-,

each Ar_1 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, a cycloalkyl group which contains between 3 and 15 carbon atoms and between 1 and 3 rings, said cycloalkyl group being optionally benzofused, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocycle group containing at least one heteroatom group selected from -O-, -S-, -SO-, -SO_2-, =N-, and -NH-, said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by: -NH_2, -CO_2H, -Cl, -F, -Br, -I, -NO_2,

-CN, =O, -OH, -perfluoro C_{1-3} alkyl, $\overset{O}{\underset{O}{\diamond}}CH_2$, or $-Q_1$;

each Q_1 is independently selected from the group consisting of:

-Ar$_1$

-R$_9$,

-T$_1$-R$_9$,   and

-$(CH_2)_{1,2,3}$-T$_1$-R$_9$;

each Q_2 is independently selected from the group consisting of -OH, -NH$_2$, -CO$_2$H, -Cl, -F, -Br, -I, -NO$_2$, -CN, -CF$_3$, and $\overset{O}{\underset{O}{\diamond}}CH_2$;

provided that when -Ar$_1$ is substituted with a Q_1 group which comprises one or more additional -Ar$_1$ groups, said additional -Ar$_1$ groups are not substituted with Q_1.

Preferred compounds of embodiment C of this invention include but are not limited to:

(Q)

;

(R)

;

(S)

;

(T)

; and

(V)

.

Preferred compounds of embodiment C of this invention are also those in which each A is independently selected from the group consisting of the α-amino acids:

alanine,
histidine,
lysine,
phenylalanine,
proline,
tyrosine,
valine,

leucine,

isoleucine,

glutamine,

methionine,

homoproline,

3-(2-thienyl) alanine, and

3-(3-thienyl) alanine.

The ICE inhibitors of another embodiment (D) of this invention are represented by the formula π:

π
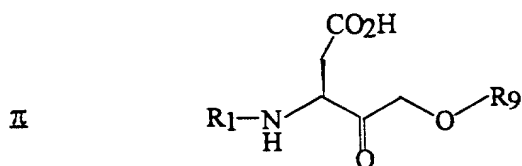
wherein:

R_1 is $R_5-(A)_p-$;

each T_1 is independently selected from the group consisting of:

$-CH=CH-$,

$-O-$,

$-S-$,

$-SO-$,

$-SO_2-$,

$-NR_{10}-$,

$-NR_{10}-CO-$,

$-CO-$,

$-O-CO-$,

$-CO-O-$,

$-CO-NR_{10}-$,

$-O-CO-NR_{10}-$,

$-NR_{10}-CO-O-$,

$-NR_{10}-CO-NR_{10}-$,

$-SO_2-NR_{10}-$,

$-NR_{10}-SO_2-$,   and

$-NR_{10}-SO_2-NR_{10}-$;

R_5 is selected from the group consisting of:

-H,

$-Ar_1$,

$-CO-Ar_1$,

$-SO_2-Ar_1$,

$-R_9$,

$-CO-R_9$,

$-CO-O-R_9$,

$-SO_2-R_9$,

$$-CO-N\begin{array}{l}/Ar_1\\\backslash R_{10},\end{array}$$

$$-SO_2-N\begin{array}{l}/Ar_1\\\backslash R_{10},\end{array}$$

$$-CO-N\begin{array}{l}/R_9\\\backslash R_{10},\end{array}\quad and$$

$$-SO_2-N\begin{array}{l}/R_9\\\backslash R_{10};\end{array}$$

each A is independently selected from the group consisiting of any α-amino acid;

p is 0, 1, 2, 3 or 4;

each R_9 is a C_{1-6} straight or branched alkyl group optionally singly or multiply substituted by -OH, -F, or =O and optionally substituted with an Ar_1 group;

each R_{10} is independently selected from the group

consisting of -H or a C_{1-6} straight or branched alkyl group;

Ar$_1$ is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, a cycloalkyl group which contains between 3 and 15 carbon atoms and between 1 and 3 rings, said cycloalkyl group being optionally benzofused, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocycle group containing at least one heteroatom group selected from -O-, -S-, -SO-, -SO$_2$-, =N-, and -NH-, said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -NH$_2$, -CO$_2$H, -Cl, -F, -Br, -I, -NO$_2$, -CH, =O, -OH, -perfluoro C_{1-3} alkyl, or

$$\underset{\diagdown\,\diagup}{\overset{\diagup\,\diagdown}{\underset{O}{\overset{O}{CH_2}}}}, \quad -R_9, \quad or \quad -T_1\text{-}R_9.$$

Preferred compounds of embodiment D of this invention are those in which R$_9$ is a C_{1-4} straight or branched alkyl substituted with Ar$_1$ when Ar$_1$ is phenyl.

Preferred compounds of embodiment D of this invention include but are not limited to:
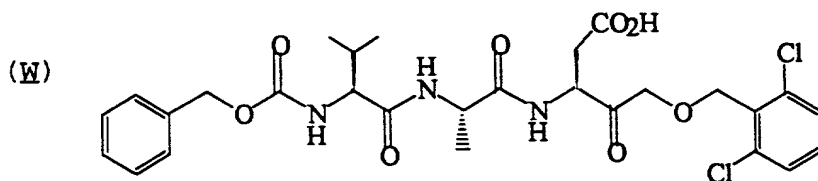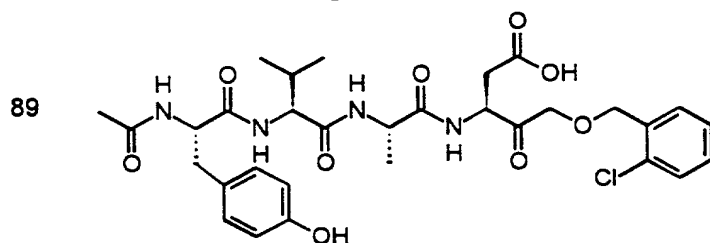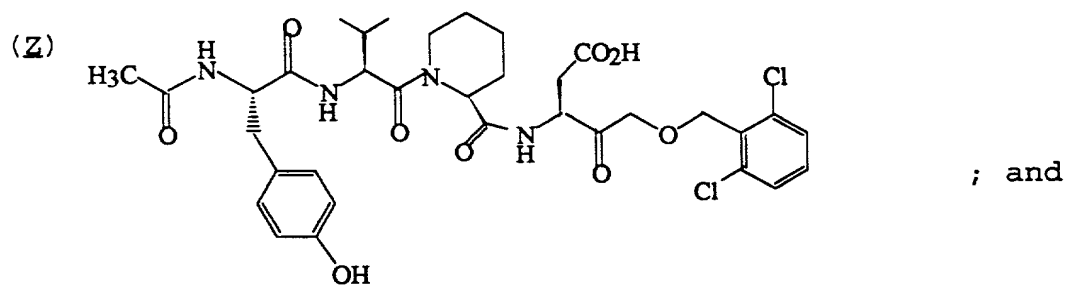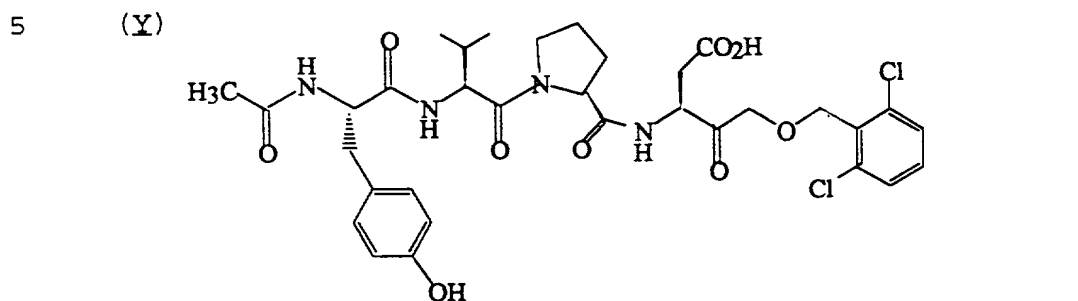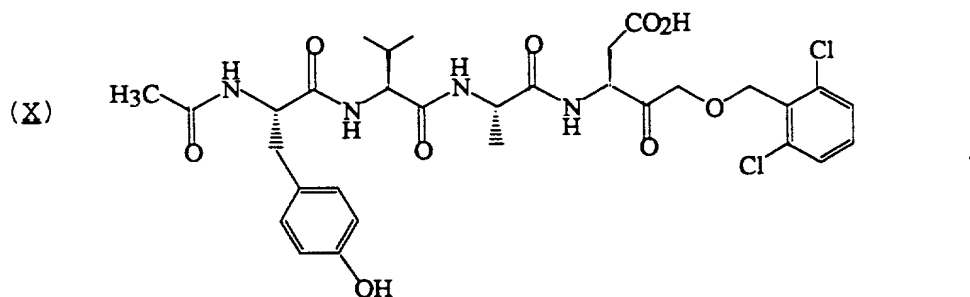
(W)

;

(**X**)

;

5   (**Y**)

;

(**Z**)

; and

89

.

10

        Preferred compounds of embodiment D of this.
invention are also those in which A is independently
selected from the group consisting of the α-amino
15   acids:

        alanine,
        histidine,

lysine,

phenylalanine,

proline,

tyrosine,

valine,

leucine,

isoleucine,

glutamine,

methionine,

homoproline,

3-(2-thienyl) alanine, and

3-(3-thienyl) alanine.

The ICE inhibitors of another embodiment (E) of this invention are represented by formula $\underline{V}$:

$\underline{V}$
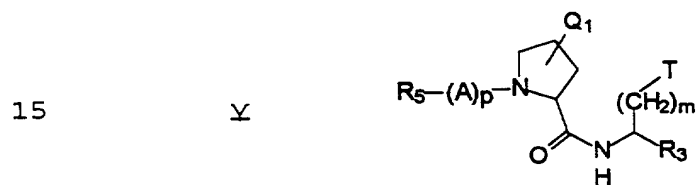
wherein:

m is 0, 1, or 2;

T is -CO_2H, or any bioisosteric replacement for -CO_2H,

R_3 is

-CN,

-COR_{13}, or

$-COCO-N\begin{array}{c} /R_5 \\ \backslash R_{10}, \end{array}$

R_5 is selected from the group consisting of:

-H,

-Ar$_1$,

-CO-Ar$_1$,

-SO$_2$-Ar$_1$,

-R$_9$,

-CO-R$_9$,

-CO-O-R$_9$,

-SO$_2$-R$_9$,

$$-CO-N\begin{smallmatrix} /Ar_1 \\ \\ \backslash R_{10}, \end{smallmatrix}$$

$$-SO_2-N\begin{smallmatrix} /Ar_1 \\ \\ \backslash R_{10}, \end{smallmatrix}$$

$$-CO-N\begin{smallmatrix} /R_9 \\ \\ \backslash R_{10}, \end{smallmatrix}\qquad \text{and}$$

$$-SO_2-N\begin{smallmatrix} /R_9 \\ \\ \backslash R_{10}; \end{smallmatrix}$$

each A is independently selected from the group consisting of any α-amino acid;

p is 2 or 3;

each R$_9$ is a C$_{1-6}$ straight or branched alkyl group optionally singly or multiply substituted by -OH, -F, or =O and optionally substituted with one Ar$_1$ group;

each T$_1$ is independently selected from the group consisting of:

-CH=CH-,

-O-,

-S-,

-SO-,

$-SO_2-$,

$-NR_{10}-$,

$-NR_{10}-CO-$,

$-CO-$,

5      $-O-CO-$,

$-CO-O-$,

$-CO-NR_{10}-$,

$-O-CO-NR_{10}-$,

$-NR_{10}-CO-O-$,

10      $-NR_{10}-CO-NR_{10}-$,

$-SO_2-NR_{10}-$,

$-NR_{10}-SO_2-$,   and

$-NR_{10}-SO_2-NR_{10}-$;

15   each R_{10} is independently selected from the group consisting of -H or a $-C_{1-6}$ straight or branched alkyl group;

each R_{13} is independently selected from the group consisting of H, R_9, Ar_2, and $CH_2T_1R_9$;

20   each Ar_1 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, a cycloalkyl group which contains between 3 and 15 carbon atoms and between 1 and 3 rings, said

25   cycloalkyl group being optionally benzofused, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocycle group containing at least one heteroatom group selected from $-O-$, $-S-$, $-SO-$, $-SO_2-$, $=N-$, and $-NH-$, said heterocycle

30   group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by $-NH_2$, $-CO_2H$,

-Cl, -F, -Br, -I, -NO$_2$, -CN, =O, -OH,

-perfluoro C$_{1-3}$ alkyl,

$$\underset{\displaystyle O}{\overset{\displaystyle O}{\diagdown\diagup}}\hspace{-0.5em}CH_2, \quad \text{or } -Q_1; \text{ and}$$

each Ar$_2$ is independently selected from the following group, in which any ring may optionally be singly or multiply substituted by -Q$_1$ and -Q$_2$:

(hh) ;

(ii) ;

(jj) ; and

(kk) ;

each Q$_1$ is independently selected from the group consisting of:

-Ar$_1$

-O-Ar$_1$

-R$_9$,

-T$_1$-R$_9$, and

-(CH$_2$)$_{1,2,3}$-T$_1$-R$_9$;

each Q$_2$ is independently selected from the group consisting of -OH, -NH$_2$, -CO$_2$H, -Cl, -F, -Br, -I, -NO$_2$, -CN, -CF$_3$, and

$$\underset{\displaystyle O}{\overset{\displaystyle O}{\diagdown\diagup}}\hspace{-0.5em}CH_2;$$

provided that when -Ar$_1$ is substituted with a Q$_1$

group which comprises one or more additional -Ar_1 groups, said additional -Ar_1 groups are not substituted with Q_1.

Preferred compounds of embodiment E of this invention include but are not limited to:

I

K

85

156

159

;

161

; and

162

.

Preferred compounds of embodiment E of this
invention are also those in which A is independently
selected from the group consisting the α-amino acids:

alanine,
histidine,
lysine,
phenylalanine,
proline,
tyrosine,
valine,
leucine,

isoleucine,

glutamine,

methionine,

homoproline,

3-(2-thienyl) alanine, and

3-(3-thienyl) alanine.

The ICE inhibitors of another embodiment (F)
of this invention are represented by formula $\underline{\delta}$:

$$\underline{\delta} \qquad R_1 \underset{\underset{H}{|}}{N} \overset{CO_2H}{\underset{\underset{O}{\|}}{C}} Ar_2$$

wherein:

    R_1 is $R_5-(A)_p-$;

    R_5 is selected from the group consisting of:

    -H,

    $-Ar_1$,

    $-CO-Ar_1$,

    $-SO_2-Ar_1$,

    $-R_9$,

    $-CO-R_9$,

    $-CO-O-R_9$,

    $-SO_2-R_9$,

$$-CO-N\begin{array}{l}/Ar_1\\\backslash R_{10},\end{array}$$

$$-SO_2-N\begin{array}{l}/Ar_1\\\backslash R_{10},\end{array}$$

$$-CO-N\begin{array}{l}/R_9\\\backslash R_{10}, \quad \text{and}\end{array}$$

$$-SO_2-N\begin{array}{l}/R_9\\\backslash R_{10};\end{array}$$

each A is independently selected from the group consisting of any α-amino acid;

p is 0, 1, 2, 3 or 4;

each R_9 is a C_{1-6} straight or branched alkyl group optionally singly or multiply substituted by -OH, -F, or =O and optionally substituted with one Ar_1 group;

each R_{10} is independently selected from the group consisting of -H or a C_{1-6} straight or branched alkyl group;

each T_1 is independently selected from the group consisting of:
  -CH=CH-,
  -O-,
  -S-,
  -SO-,

each Ar_1 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, a cycloalkyl group which contains between 3 and 15 carbon atoms and between 1 and 3 rings, said cycloalkyl group being optionally benzofused, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocycle group containing at least one heteroatom group selected from -O-, -S-, -SO-, -SO$_2$-, =N-, and -NH-, said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -NH$_2$, -CO$_2$H, -Cl, -F, -Br, -I, -NO$_2$, -CN, =O, -OH,

-perfluoro C_{1-3} alkyl,

$$\begin{array}{c} O \\ / \ \backslash \\ \quad\quad CH_2, \text{ or } -Q_1; \text{ and} \\ \backslash \ / \\ O \end{array}$$

each Ar_2 is independently selected from the following group, in which any ring may optionally be singly or multiply substituted by $-Q_1$ and $-Q_2$:

(ii)

;

(jj)

; and

(kk)

;

each Q_1 is independently selected from the group consisting of:

-Ar_1

-O-Ar_1

-R_9,

-T_1-R_9,   and

-$(CH_2)_{1,2,3}$-T_1-R_9;

each Q_2 is independently selected from the group consisting of -OH, -NH$_2$, -CO$_2$H, -Cl, -F, -Br, -I, -NO$_2$, -CN, -CF$_3$, and

$$\begin{array}{c} O \\ / \ \backslash \\ \quad\quad CH_2; \\ \backslash \ / \\ O \end{array}$$

provided that when -Ar_1 is substituted with a Q_1 group which comprises one or more additional -Ar_1

groups, said additional -Ar₁ groups are not substituted with Q₁;

each X is independently selected from the group consisting of =N-, and =CH-; and

each Y is independently selected from the group consisting of -O-, -S-, and -NH.

Preferred compounds of emvodiment F of this invention include but are not limited to:

144

145

146

147

148

149

150 ;

151 ;

5

152 ;

153 ;

154 ;

155 ; and

163 .

10
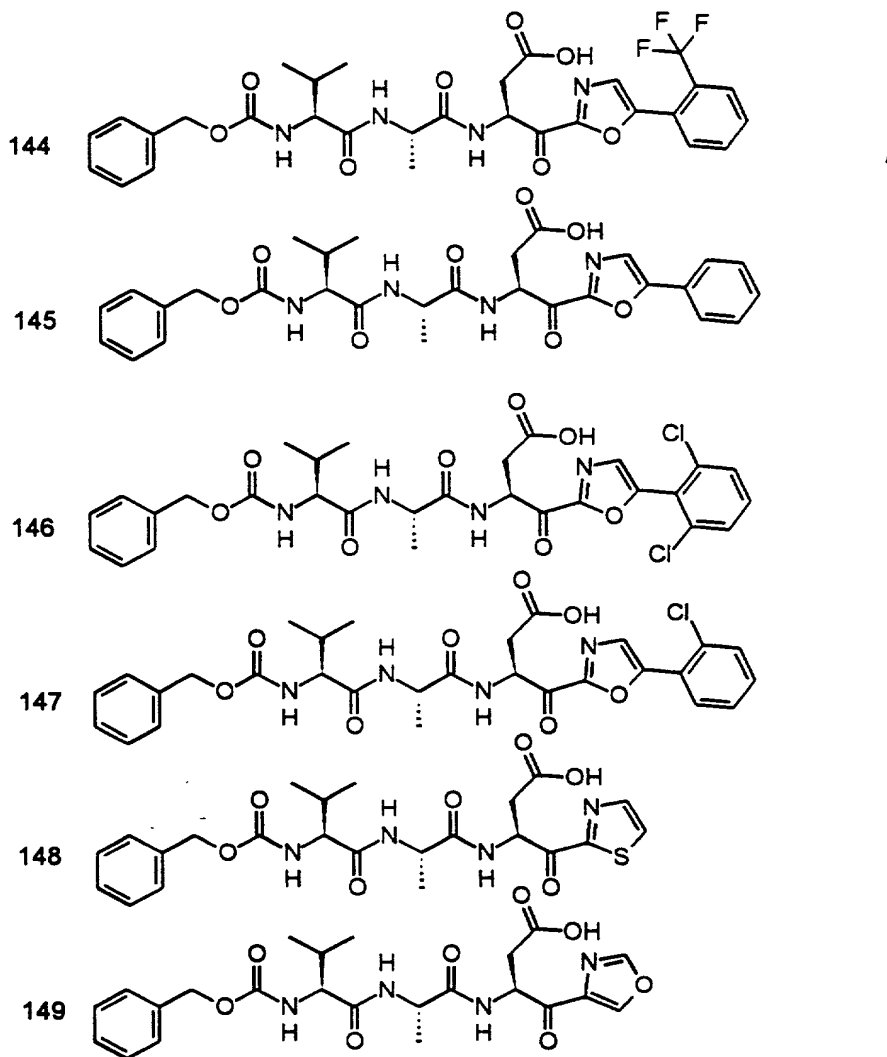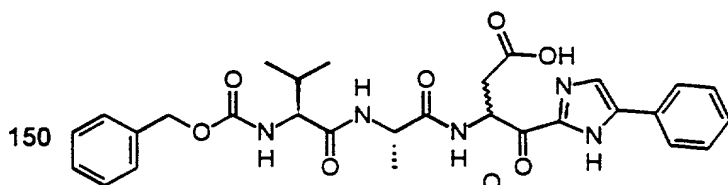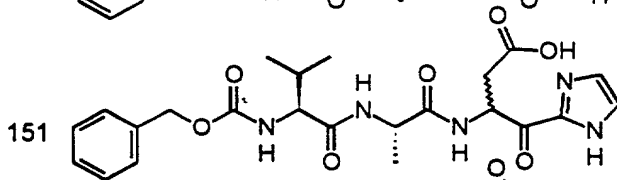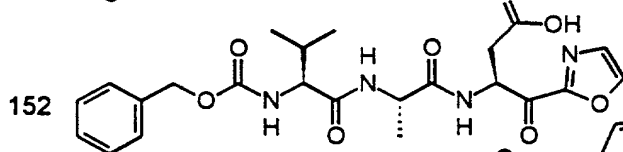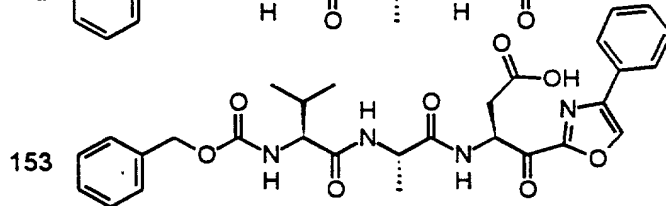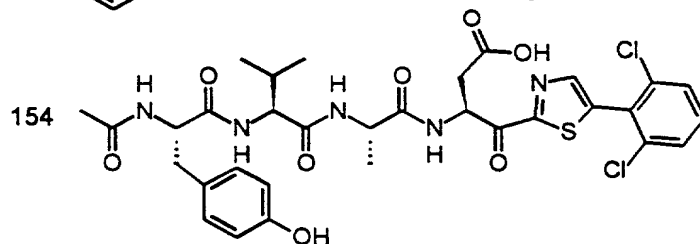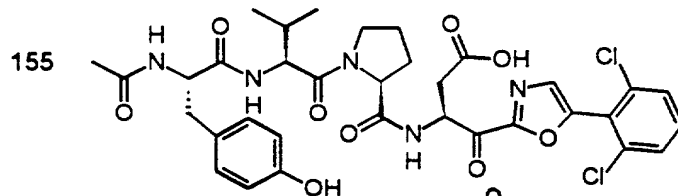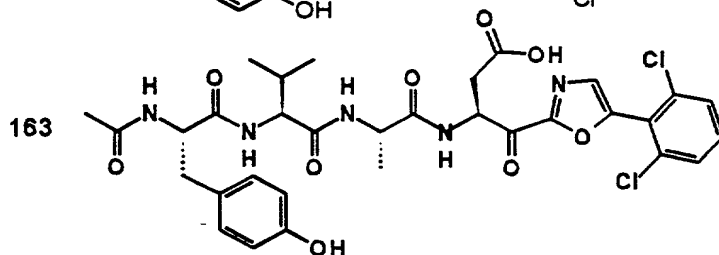
Preferred compounds of embodiment F of this
invention are also those in which A is independently
15   selected from the group consisting the α-amino acids:
alanine,

histidine,

lysine,

phenylalanine,

proline,

5   tyrosine,

valine,

leucine,

isoleucine,

glutamine,

10   methionine,

homoproline,

3-(2-thienyl) alanine, and

3-(3-thienyl) alanine.

The compounds of this invention having a

15   molecular weight of less than or equal to about 700
Daltons, and more preferably between about 400 and 600
Daltons, are preferred. These preferred compounds may
be readily absorbed by the bloodstream of patients upon
oral administration. This oral availability makes such

20   compounds excellent agents for orally-administered
treatment and prevention regimens against IL-1 mediated
diseases.

The ICE inhibitors of this invention may be
synthesized using conventional techniques.

25   Advantageously, these compounds are conveniently
synthesized from readily available starting materials.
The compounds of this invention are among the
most readily synthesized ICE inhibitors known.
Previously described ICE inhibitors often contain four

30   or more chiral centers and numerous peptide linkages.
The relative ease with which the compounds of this
invention can be synthesized represents an enormous
advantage in the large scale production of these

compounds.

It should be understood that the compounds of
this invention may exist in various equilibrium forms,
depending on conditions including choice of solvent,
5   pH, and others known to the practitioner skilled in the
art. All such forms of these compounds are expressly
included in the present invention. In particular, many
of the compounds of this invention, especially those
which contain aldehyde or ketone groups in R_3 and
10 carboxylic acid groups in T, may take hemi-ketal (or
hemi-acetal) or hydrated forms, as depicted below:

(EQ1)

$$R_1-\underset{H}{N}-X_1 \begin{array}{c} (CH_2)m-\overset{O}{\overset{\|}{C}}-OH \\ \\ (CH_2)g-\underset{OH}{\overset{OH}{C}}-R_{13} \end{array} \rightleftharpoons R_1-\underset{H}{N}-X_1 \begin{array}{c} (CH_2)m-\overset{O}{\overset{\|}{C}}-OH \\ \\ (CH_2)g-\overset{O}{\underset{\|}{C}}-R_{13} \end{array} \rightleftharpoons R_1-\underset{H}{N}-X_1 \begin{array}{c} (CH_2)m-\overset{O}{\overset{\|}{C}} \\ O \\ (CH_2)g-\underset{OH}{\overset{}{C}}-R_{13} \end{array}$$

Hydrated Form   Hemi-ketal or
                                                Hemi-acetal For
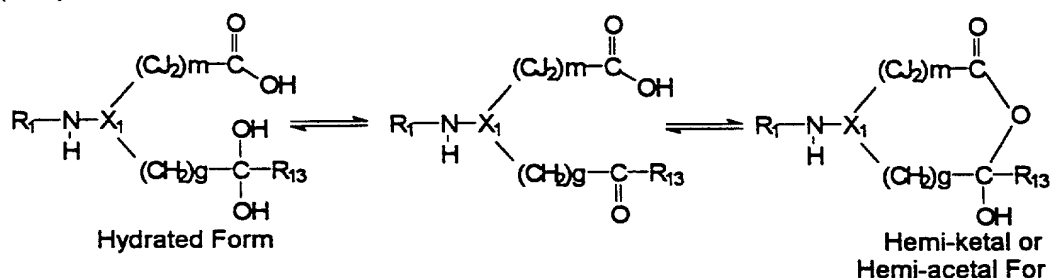
Depending on the choice of solvent and other
conditions known to the practitioner skilled in the
15 art, compounds of this invention may also take acyloxy
ketal, acyloxy acetal, ketal or acetal form:

(EQ2)

$$R_1-\underset{H}{N}-X_1 \begin{array}{c} (CH_2)m-\overset{O}{\overset{\|}{C}} \\ O \\ (CH_2)g-\underset{OR}{\overset{}{C}}-R_{13} \end{array} \rightleftharpoons R_1-\underset{H}{N}-X_1 \begin{array}{c} (CH_2)m-\overset{O}{\overset{\|}{C}}-OH \\ \\ (CH_2)g-\overset{O}{\underset{\|}{C}}-R_{13} \end{array} \rightleftharpoons R_1-\underset{H}{N}-X_1 \begin{array}{c} (CH_2)m-\overset{O}{\overset{\|}{C}}-OH \\ OR \\ (CH_2)g-\underset{OR}{\overset{}{C}}-R_{13} \end{array}$$

Acyloxy Ketal or   Ketal or Acetal For
Acyloxy Acetal Form
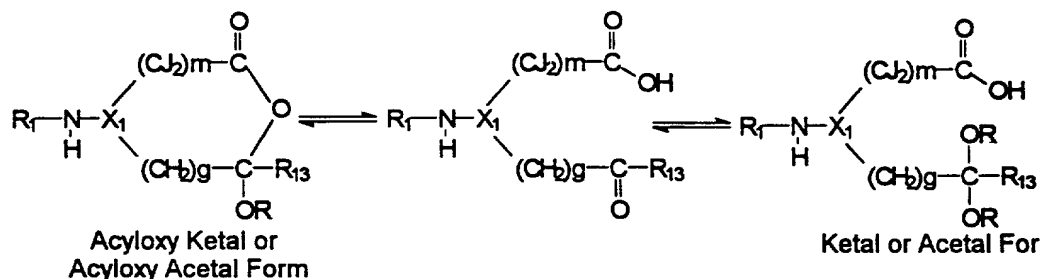
In addition, it should be understood that the
equilibrium forms of the compounds of this invention
20 may include tautomeric forms. All such forms of these

compounds are expressly included in the present
invention.

It should be understood that the compounds of
this invention may be modified by appropriate
5   functionalities to enhance selective biological
properties. Such modifications are known in the art
and include those which increase biological penetration
into a given biological system (e.g., blood, lymphatic
system, central nervous system), increase oral
10   availability, increase solubility to allow
administration by injection, alter metabolism and alter
rate of excretion. In addition, the compounds may be
altered to pro-drug form such that the desired compound
is created in the body of the patient as the result of
15   the action of metabolic or other biochemical processes
on the pro-drug. Some examples of pro-drug forms
include ketal, acetal, oxime, and hydrazone forms of
compounds which contain ketone or aldehyde groups,
especially where they occur in the R_3 group of the
20   compounds of this invention.

The compounds of this invention are excellent
ligands for ICE. Accordingly, these compounds are
capable of targeting and inhibiting events in IL-1
mediated diseases, such as the conversion of precursor
25   IL-1ß to mature IL-1ß and, thus, the ultimate activity
of that protein in inflammatory diseases, autoimmune
diseases and neurodegenerative diseases. For example,
the compounds of this invention inhibit the conversion
of precursor IL-1ß to mature IL-1ß by inhibiting ICE.
30   Because ICE is essential for the production of mature
IL-1, inhibition of that enzyme effectively blocks
initiation of IL-1 mediated physiological effects and
symptoms, such as inflammation, by inhibiting the
production of mature IL-1. Thus, by inhibiting IL-1ß
35   precursor activity, the compounds of this invention

effectively function as IL-1 inhibitors.

The compounds of this invention may be employed in a conventional manner for the treatment of diseases which are mediated by IL-1. Such methods of treatment, their dosage levels and requirements may be selected by those of ordinary skill in the art from available methods and techniques. For example, a compound of this invention may be combined with a pharmaceutically acceptable adjuvant for administration to a patient suffering from an IL-1 mediated disease in a pharmaceutically acceptable manner and in an amount effective to lessen the severity of that disease.

Alternatively, the compounds of this invention may be used in compositions and methods for treating or protecting individuals against IL-1 mediated diseases over extended periods of time. The compounds may be employed in such compositions either alone or together with other compounds of this invention in a manner consistent with the conventional utilization of ICE inhibitors in pharmaceutical compositions. For example, a compound of this invention may be combined with pharmaceutically acceptable adjuvants conventionally employed in vaccines and administered in prophylactically effective amounts to protect individuals over an extended period time against IL-1 mediated diseases.

The compounds of this invention may also be co-administered with other ICE inhibitors to increase the effect of therapy or prophylaxis against various IL-1-mediated diseases.

In addition, the compounds of this invention may be used in combination either conventional anti-inflammatory agents or with matrix metalloprotease inhibitors, lipoxygenase inhibitors and antagonists of cytokines other than IL-1ß.

The compounds of this invention can also be administered in combination with immunomodulators (e.g., bropirimine, anti-human alpha interferon antibody, IL-2, GM-CSF, methionine enkephalin, interferon alpha, diethyldithiocarbamate, tumor necrosis factor, naltrexone and rEPO) or with prostaglandins, to prevent or combat IL-1-mediated disease symptoms such as inflammation.

When the compounds of this invention are administered in combination therapies with other agents, they may be administered sequentially or concurrently to the patient. Alternatively, pharmaceutical or prophylactic compositions according to this invention may be comprised of a combination of an ICE inhibitor of this invention and another therapeutic or prophylactic agent.

Pharmaceutical compositions of this invention comprise any of the compounds of the present invention, and pharmaceutically acceptable salts thereof, with any pharmaceutically acceptable carrier, adjuvant or vehicle. Pharmaceutically acceptable carriers, adjuvants and vehicles that may be used in the pharmaceutical compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers,

polyethylene glycol and wool fat.

The pharmaceutical compositions of this invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. We prefer oral administration. The pharmaceutical compositions of this invention may contain any conventional non-toxic pharmaceutically-acceptable carriers, adjuvants or vehicles. The term parenteral as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intra-articular, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques.

The pharmaceutical compositions may be in the form of a sterile injectable preparation, for example, as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions

or suspensions may also contain a long-chain alcohol diluent or dispersant such as Ph. Helv or a similar alcohol.

5   The pharmaceutical compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, and aqueous suspensions and solutions. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are administered orally, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents may be added.

The pharmaceutical compositions of this invention may also be administered in the form of suppositories for rectal administration. These compositions can be prepared by mixing a compound of this invention with a suitable non-irritating excipient which is solid at room temperature but liquid at the rectal temperature and therefore will melt in the rectum to release the active components. Such materials include, but are not limited to, cocoa butter, beeswax and polyethylene glycols.

Topical administration of the pharmaceutical compositions of this invention is especially useful when the desired treatment involves areas or organs readily accessible by topical application. For application topically to the skin, the pharmaceutical composition should be formulated with a suitable ointment containing the active components suspended or

dissolved in a carrier. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petroleum, white petroleum, propylene glycol, polyoxy-ethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutical composition can be formulated with a suitable lotion or cream containing the active compound suspended or dissolved in a carrier. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water. The pharmaceutical compositions of this invention may also be topically applied to the lower intestinal tract by rectal suppository formulation or in a suitable enema formulation. Topically-transdermal patches are also included in this invention.

The pharmaceutical compositions of this invention may be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

The IL-1 mediated diseases which may be treated or prevented by the compounds of this invention include, but are not limited to, inflammatory diseases, autoimmune diseases and neurodegenerative diseases.

Inflammatory diseases which may be treated or prevented include, for example, septic shock, septicemia, and adult respiratory distress syndrome. Target autoimmune diseases include, for example, rheumatoid, arthritis, systemic lupus erythematosus,

scleroderma, chronic thyroiditis, Graves' disease, autoimmune gastritis, insulin-dependent diabetes mellitus, autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, chronic active

5   hepatitis, myasthenia gravis and multiple sclerosis. And target neurodegenerative diseases include, for example, amyotrophic lateral sclerosis, Alzheimer's disease, Parkinson's disease, and primary lateral sclerosis. The ICE inhibitors of this invention may

10   also be used to promote wound healing. And the ICE inhibitors of this invention may be used to treat infectious diseases.

      Although this invention focuses on the use of the compounds disclosed herein for preventing and

15   treating IL-1-mediated diseases, the compounds of this invention can also be used as inhibitory agents for other cysteine proteases.

      The compounds of this invention are also useful as commercial reagents which effectively bind to

20   ICE or other cysteine proteases. As commercial reagents, the compounds of this invention, and their derivatives, may be used to block proteolysis of a target peptide or may be derivatized to bind to a stable resin as a tethered substrate for affinity

25   chromatography applications. These and other uses which characterize commercial cystine protease inhibitors will be evident to those of ordinary skill in the art.

      In order that this invention be more fully

30   understood, the following examples are set forth. These examples are for the purpose of illustration only and are not to be construed as limiting the scope of the invention in any way.

Example 1

The following example demonstrates a process of drug design which embodies the present invention:

Step 1) Pick 2 hydrogen bonding moieties of ICE, here, the backbone C=O and N-H of Arg-341.

Step 2) Pick a scaffold, here, a pyridone derivative, and confirm that the hydrogen bonding moieties of the scaffold are capable of forming satisfactory hydrogen bonds with the hydrogen bonding moieties selected in step 1. This confirmation is performed by using molecular mechanics techniques to minimize the scaffold fragment in the context of the active site of ICE.

(Z1)
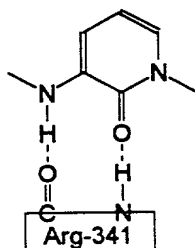
Step 3) Pick a hydrophobic pocket, here, S2, as next target and a hydrophobic moiety, here, benzene. Minimize the benzene group within the S2 pocket to assure that substantial hydrophobic overlap is obtained.

(Z2)
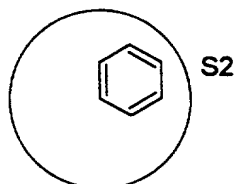
Step 4) Pick another hydrophobic pocket, here, S4, as the next target and a hydrophobic moiety,

here, benzene. Minimize the benzene group within
the S4 pocket to ensure that substantial
hydrophobic overlap is obtained.

(Z3) S4
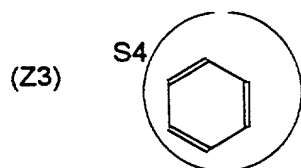
5   Step 5) Fill the S1 polar pocket with an
     electronegative moiety, here, a carboxylate
     sidechain provided by aspartic acid in which the
     C-terminus has been reduced to an aldehyde.
     Minimize to ensure that the carboxylate sidechain
10   retains a favorable electrostatic interaction with
     the S1 polar pocket.

(Z4) H$_2$N   CHO

S1

CO$_2^-$
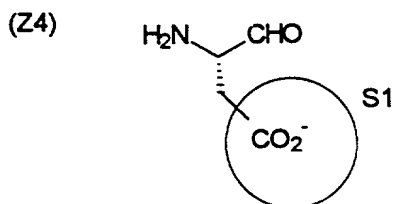
     Step 6) Link the scaffold with the moieties from
     steps 3, 4, and 5, preferably using the minimum
     number of bonds consistent with a chemically
15   reasonable structure. Minimize the entire
     composite molecule in the active site of ICE.

(Z5)
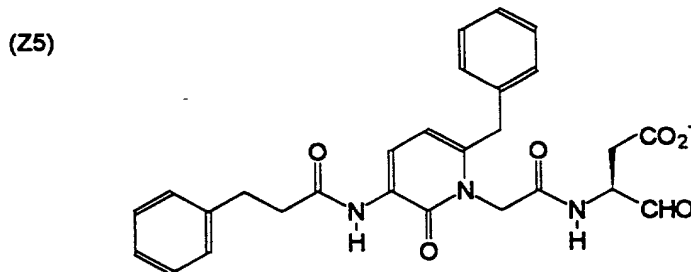
Step 7)   Evaluate the energy of the molecule when it has the conformation necessary for binding to ICE.   Then minimize and reevaluate the energy -- this is the free conformation energy.   The strain energy for binding of the potential inhibitor to ICE is the difference between the free conformation energy and the bound conformation energy.   The strain energy should be less than about 10 kcal/mol.   In this case the bound conformation energy is -1.6 kcal/mol and the free conformation energy is -11.7 kcal/mol, for a strain energy of 10.1 kcal/mol.

Step 8)   The inhibitor designed using the above steps has been made and has been show to have a K_i of 150 nM.

Example 2

We obtained inhibition constants (K_i) and IC_{50} values for several compounds of this invention using the three methods described below:

1.   Enzyme assay with UV-visible substrate

This assay is run using an Succinyl-Tyr-Val-Ala-Asp-pNitroanilide substrate.   Synthesis of analogous substrates is described by L. A. Reiter (Int. J. Peptide Protein Res. 43, 87-96 (1994)).   The assay mixture contains:

65 μl buffer (10mM Tris, 1 mM DTT, 0.1% CHAPS @pH 8.1)
10 μl ICE (50 nM final concentration to give a rate of ¯1mOD/min)
 5 μl DMSO/Inhibitor mixture
20 μl 400μM Substrate (80 μM final concentration)
100μl total reaction volume

The visible ICE assay is run in a 96-well microtiter plate.   Buffer, ICE and DMSO (if inhibitor

is present) are added to the wells in the order listed. The components are left to incubate at room temperature for 15 minutes starting at the time that all components are present in all wells. The microtiter plate reader

5   is set to incubate at 37°C. After the 15 minute incubation, substrate is added directly to the wells and the reaction is monitored by following the release of the chromophore (pNA) at 405 - 603 nm at 37°C for 20 minutes. A linear fit of the data is performed and the

10   rate is calculated in mOD/min. DMSO is only present during experiments involving inhibitors, buffer is used to make up the volume to 100 μl in the other experiments.

2.   Enzyme Assay with Fluorescent Substrate

15   This assay is run essentially according to Thornberry et al. (Nature 356: 768-774 (1992)), using substrate 17 referenced in that article. The substrate is: Acetyl-Tyr-Val-Ala-Asp-amino-4-methylcoumarin (AMC). The following components are mixed:

20   65 μl buffer(10mM Tris,1mM DTT, 0.1% CHAPS @pH8.1)
       10 μl ICE (2 - 10 nM final concentration)
        5 μl DMSO/inhibitor solution
       20 μl 150 μM Substrate (30 μM final)
       100μl total reaction volume

25   The assay is run in a 96 well microtiter plate. Buffer and ICE are added to the wells. The components are left to incubate at 37°C for 15 minutes in a temperature-controlled wellplate. After the 15 minute incubation, the reaction is started by adding

30   substrate directly to the wells and the reaction is monitored @37°C for 30 minutes by following the release of the AMC fluorophore using an excitation wavelength for 380 nm and an emission wavelength of 460 nm. A linear fit of the data for each well is performed and a

rate is determined in fluorescence units per second.

For determination of enzyme inhibition constants (K_i) or the mode of inhibition (competitive, uncompetitive or noncompetitive), the rate data determined in the enzyme assays at varying inhibitor concentrations are computer-fit to standard enzyme kinetic equations (see I. H. Segel, Enzyme Kinetics, Wiley-Interscience, 1975).

3.   Cell assay

IL-1ß Assay with a Mixed Population of Human Peripheral Blood Mononuclear Cells (PBMC) or Enriched Adherent Mononuclear Cells

Processing of pre-IL-1ß by ICE can be measured in cell culture using a variety of cell sources. Human PBMC obtained from healthy donors provides a mixed population of lymphocyte subtypes and mononuclear cells that produce a spectrum of interleukins and cytokines in response to many classes of physiological stimulators. Adherent mononuclear cells from PBMC provides an enriched source of normal monocytes for selective studies of cytokine production by activated cells.

Experimental Procedure:

An initial dilution series of test compound in DMSO or ethanol is prepared, with a subsequent dilution into RPMI-10% FBS media (containing 2 mM L-glutamine, 10 mM HEPES, 50 U and 50 ug/ml pen/strep) respectively to yield drugs at 4x the final test concentration containing 0.4% DMSO or 0.4% ethanol. The final concentration of DMSO is 0.1% for all drug dilutions. A concentration titration which brackets the apparent K_i for a test compound determined in an ICE inhibition assay is generally used for the primary compound screen.

We generally test 5-6 compound dilutions and

have performed the cellular component of the assay in duplicate, with duplicate ELISA determinations on each cell culture supernatant.

PBMC Isolation and IL-1 Assay:

Buffy coat cells isolated from one pint human blood (yielding 40-45 ml final volume plasma plus cells) are diluted with media to 80 ml and LeukoPREP separation tubes (Becton Dickinson) are each overlaid with 10 ml of cell suspension. After 15 min centrifugation at 1500-1800 xg, the plasma/media layer is aspirated and then the mononuclear cell layer is collected with a Pasteur pipette and transferred to a 15 ml conical centrifuge tube (Corning). Media is added to bring the volume to 15 ml, gently mix the cells by inversion and centrifuge at 300 xg for 15 min. Resuspend the PBMC pellet in a small volume of media, count cells and adjust to 6 x 10^6 cells/ml.

For the cellular assay, add 1.0 ml of the cell suspension to each well of a 24-well flat bottom tissue culture plate (Corning), 0.5 ml test compound dilution and 0.5 ml LPS solution (Sigma #L-3012; 20 ng/ml solution prepared in complete RPMI media; final LPS concentration 5 ng/ml). The 0.5 ml additions of test compound and LPS are usually sufficient to mix the contents of the wells. Three control mixtures are run per experiment, with either LPS alone, solvent vehicle control, and/or additional media to adjust the final culture volume to 2.0 ml. The cell cultures are incubated for 16-18 hr at 37°C in the presence of 5% CO_2.

At the end of the incubation period, cells are harvested and transferred to 15 ml conical centrifuge tubes. After centrifugation for 10 min at 200 xg, supernatants are harvested and transferred to 1.5 ml Eppendorf tubes. It may be noted that the cell

pellet may be utilized for a biochemical evaluation of pre-IL-1ß and/or mature IL-1ß content in cytosol extracts by western blotting or ELISA with pre-IL-1ß specific antisera.

5   Isolation of Adherent Mononuclear cells:

PBMC are isolated and prepared as described above. Media (1.0 ml) is first added to wells followed by 0.5 ml of the PBMC suspension. After a one hour incubation, plates are gently shaken and nonadherent

10   cells aspirated from each well. Wells are then gently washed three times with 1.0 ml of media and final resuspended in 1.0 ml media. The enrichment for adherent cells generally yields $2.5\text{-}3.0 \times 10^5$ cells per well. The addition of test compounds, LPS, cell

15   incubation conditions and processing of supernatants proceeds as described above.

                 ELISA:

We have used Quantikine kits (R&D Systems) for measurement of mature IL-1ß. Assays are performed

20   according to the manufacturer's directions. Mature IL-1ß levels of about 1-3 ng/ml in both PBMC and adherent mononuclear cell positive controls are observed. ELISA assays are performed on 1:5, 1:10 and 1:20 dilutions of supernatants from LPS-positive

25   controls to select the optimal dilution for supernatants in the test panel.

The inhibitory potency of the compounds can be represented by an IC_{50} value, which is the concentration of inhibitor at which 50% of mature IL-1ß

30   is detected in the supernatant as compared to the positive controls.

The following K_i and IC_{50} values were determined for compounds A through N using the indicated assays. Structures for compounds A through N

35   follow this table.

Compound	K_i (μM), by indicated assay:		
	UV-visible K_i (μM)	Fluorescence K_i (μM)	Cell IC_{50} (μM)
A	5.5		25.0
B	8.6		20.0
C	10		>30
D	4.7		
E	3.2		
F	0.15		2 - 4
G	4.8		
H	0.023	0.0047	6 - 11
I	0.0072	0.0052	2.6
J	0.012	0.0039	5 - 7
K	0.010	0.002	2 - 11
L	0.014		
M	0.15		
N	0.95		

Structures of compounds A through N:

A

B

C

D

E

F

G

5 H

I
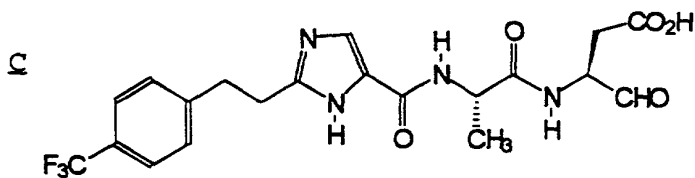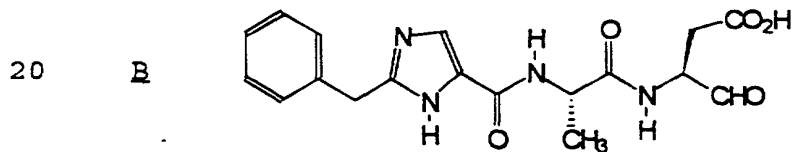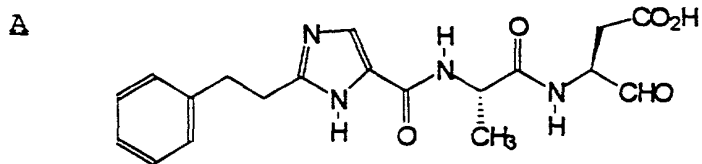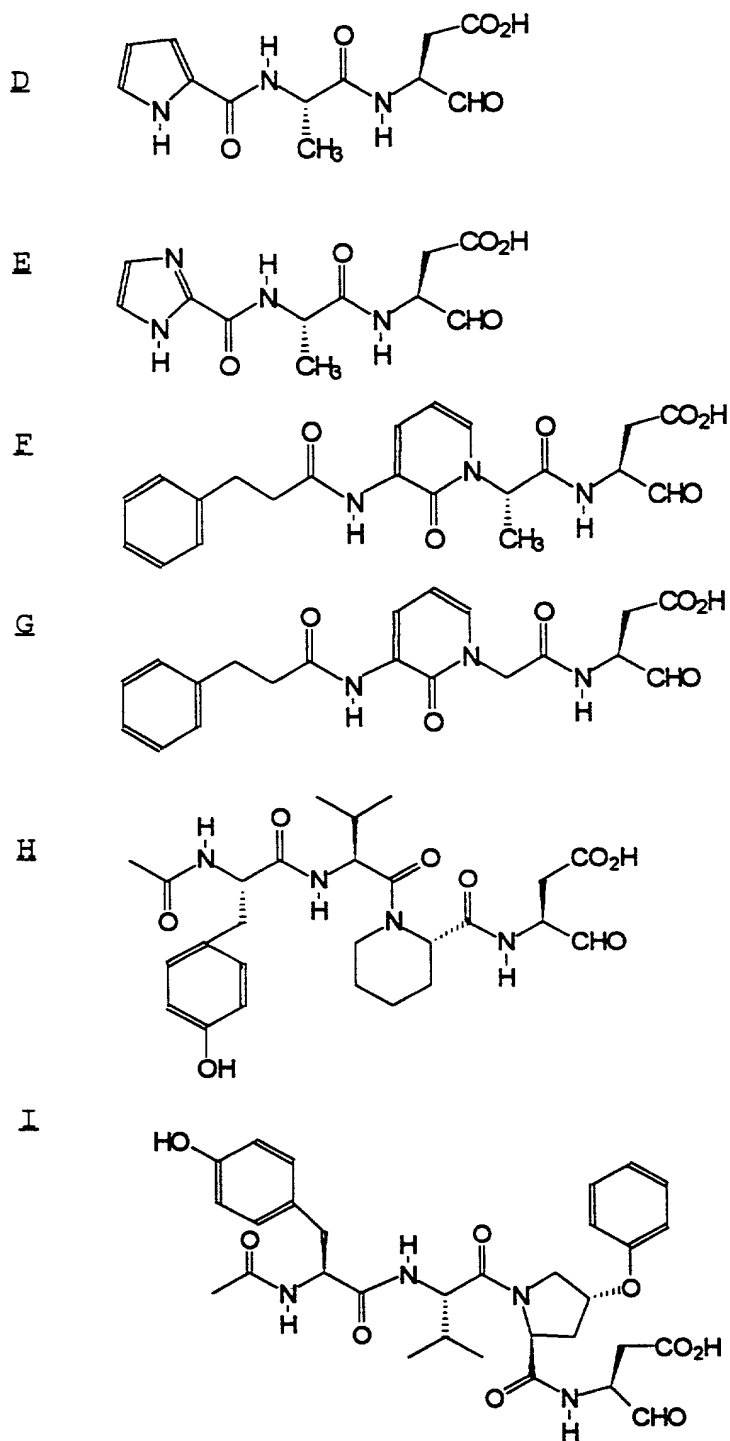
J
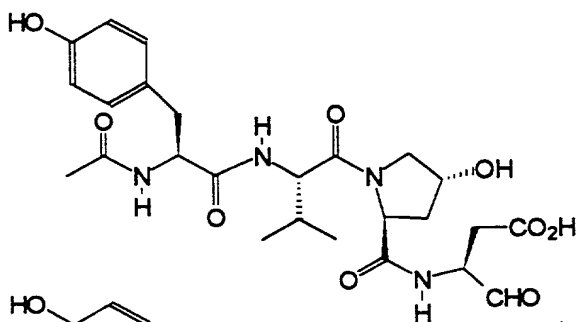
K
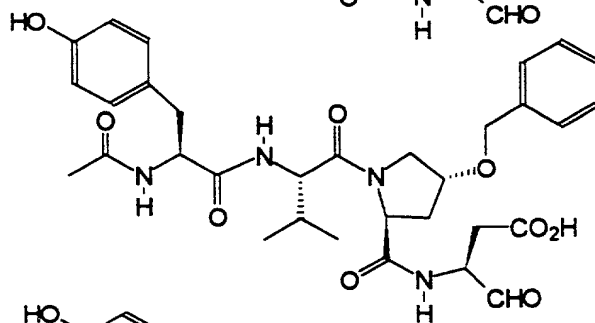
L
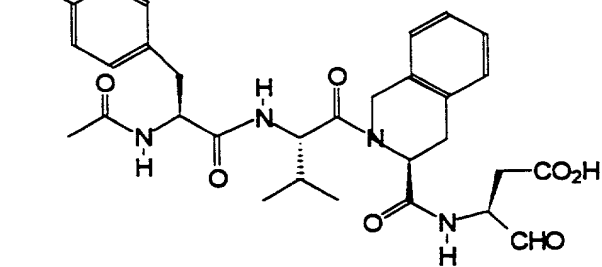
M
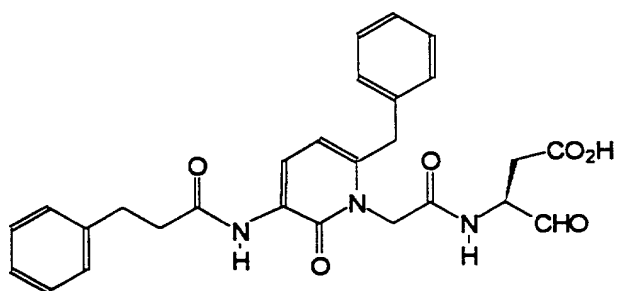
5 N
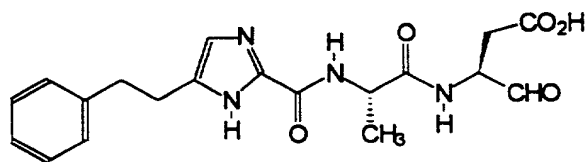
Example 3

Compounds of Example 2 were synthesized as follows:

H. N-(N-Acetyl-tyrosinyl-valinyl-pipecolyl)-3-amino-4-oxobutanoic acid.

Step A.   N-(N-tert-Butoxycarbonylpipecolyl)-4-amino-5-benzyloxy-2-oxotetrahydrofuran.

Reaction of N-tert-butoxycarbonylpipecolic acid (460 mg, 2.0 mmol) and N-allyloxycarbonyl-4-amino-5-benzyloxy-2-oxotetrahydrofuran (530 mg, 1.82 mmol) was carried out by a method analogous to that reported by Chapman (Bioorg. & Med. Chem. Lett. 1992, 2, 613-618.) to give 654 mg of the title compound.

^{1}H NMR (500 MHz, CDCl$_3$ (existing as rotamers)) δ 7.35 (m, 5H), 6.88 (br. s, 1H), 4.9-4.45(m, 4H), 3.95 (br. m, 2H), 3.06 (m, 1H), 2.9 (m, 1H), 2.7 (br. m, 1H), 2.45 (m, 1H), 2.2 (m, 1H), 1.7-1.5 (m, 3H), 1.45 (two s, 9H).

Step B.   N-Pipecolyl-4-amino-5-benzyloxy-2-oxotetrahydrofuran.

N-(N-tert-Butoxycarbonylpipecolyl)-4-amino-5-benzyloxy-2-oxo-tetrahydrofuran (654 mg) was dissolved in 15 ml of 25% trifluoroacetic acid in dichloromethane and stirred at room temperature. The mixture was concentrated to give a gummy residue. The residue was dissolved in dichloromethane and washed with 10% sodium bicarbonate. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated to give 422 mg of the title compound as a beige solid.

^{1}H NMR (500 MHz, CDCl$_3$) δ 7.38 (m, 5H), 7.15 (d, 1H), 5.55 (d, 1H), 4.95-4.8 (m, 1H), 4.78 (m, 1H), 4.65 (d, 1H), 4.45 (m, 1H), 3.2 (m, 0.5H), 3.05 (m, 0.5H), 2.95 (m, 0.5H), 2.85 (m, 0.5H), 2.65 (m, 1H), 2.55-2.38(m, 1H), 1.95 (m, 1H), 1.8 (m, 1H), 1.6 (m, 2H), 1.38 (m, 2H).

Step C. N-(N-Acetyl-tyrosinyl-valinyl-pipecolyl)-4-amino-5-benzyloxy-2-oxotetrahydrofuran.

N-Acetyl-tyrosinyl-valine (464 mg, 1.44 mmol) and N-Pipecolyl-4-amino-5-benzyloxy-2-oxotetrahydrofuran (412 mg, 1.3 mmol) were dissolved in 5 ml each of dimethylformamide and dichloromethane and cooled to 0°C. To the cooled solution was added 1-hydroxybenzotriazole (HOBT; 210 mg, 1.56 mmol) followed by the addition of 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (EDC; 326 mg, 1.7 mmol). After stirring for 18 hours, the mixture was diluted with ethyl acetate and washed with water, 10% sodium hydrogen sulfate, 10% sodium bicarbonate, and water. The organic layer was concentrated to give a crude solid that was purified by flash chromatography (SiO$_2$) eluting with 94:6:1 (dichloromethane:isopropanol:pyridine) to give 370 mg of the title compound.

^{1}H NMR (500 MHz, CD$_3$OD (existing as diastereomers as well as rotamers)) δ 7.35 (m, 5H), 7.05 (m, 2H), 6.68 (m, 2H), 5.65 & 5.25 (m, 1H), 4.9-3.95 (m, 8H), 3.4-2.6 (m, 4H), 2.5-2.1 (m, 1H), 1.98 (s, 1H), 1.9 (s, 1H), 1.85 (s, 1H), 1.8-1.6 (m, 2H), 1.55-1.3 (m, 4H), 0.95-0.85 (m, 6H).

Step D.   N-(N-Acetyl-tyrosinyl-valinyl-pipecolyl)-
          3-amino-4-oxobutanoic acid.

          To a solution of 100 mg of N-(N-Acetyl-
tyrosinyl-valinyl-pipecolyl)-4-amino-5-benzyloxy-2-
5   oxotetrahydrofuran in 10 ml of methanol was added 60 mg
of Pd(OH)$_2$ on carbon and the mixture placed under an
atmosphere of hydrogen via a balloon. The mixture was
filtered through Celite and concentrated providing a
white solid. This crude solid was dissolved in 2 ml of
10   methanol and triturated with diethyl ether affording 26
mg of the title compound.

          ^{1}H NMR (500 MHz, CD$_3$OD(existing as diastereomers
as well as rotamers)) δ 7.1 (m, 2H), 6.7 (m, 2H), 5.2
(br. m, 1H), 4.8-3.6 (m, 6H), 3.2-2.5 (m, 4H), 2.5-2.1
15   (m, 1H), 1.95 (three s, 3H), 1.9-1.3 (m, 6H), 1.1-0.7
(m, 6H).

          The following compounds were prepared by a
method analogous to that reported for H:

J. N-[N-Acetyl-tyrosinyl-valinyl-(4-hydroxyprolinyl)]-
20   3-amino-4-oxobutanoic acid

          Substitute N-tert-butoxycarbonyl-4-
benzyloxyproline for N-tert-butoxycarbonylpipecolic
acid.

L. N-[2-(N-Acetyl-tyrosinyl-valinyl)-(S)-1,2,3,4-
25   tetrahydroisoquinoline-3-carbonyl]-3-amino-
oxobutanoic acid

          Substitute (S)-N-tert-butoxycarbonyl-1,2,3,4-
tetrahydroisoquinoline-3-carboxylic acid for N-tert-
butoxycarbonylpipecolic acid.

I. <u>N-(N-Acetyl-tyrosinyl-valinyl-(4-phenoxyprolinyl))-</u>
<u>3-amino-4-oxobutanoic acid</u>.

Step A.   <u>N-tert-Butoxycarbonyl-4-phenoxyproline</u>
<u>methyl ester</u>.

5   To a cooled solution (0° C) of N-tert-butoxy-
cis-4-hydroxyproline (2-0 g, 8.15 mmol), phenol (0.77
g, 8.15 mmol), and triphenylphosphine (2.14 g, 8.15
mmol) in 20 ml of tetrahydrofuran was added diethyl
azodicarboxylate (1.4 ml, 9 mmol) dropwise over 30
10   minutes. The reaction was stirred at room temperature
for 16 hrs. then concentrated to give a viscous
residue. The crude residue was purified by flash
chromatography (SiO$_2$) eluting with 3:7 (ethyl
acetate:hexane) to give 1.89 g of the title compound.

15   ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.3 (m, 2H), 6.95 (m,
1H), 6.85 (d, 2H), 4.9 (m br., 1H), 4.55-4.15 (m, 2H),
3.88-3.65 (m, 1H), 3.70 (s, 3H), 2.58 (m, 1H), 2.22 (m,
1H), 1.4 (3 x s, 9H).

Step B.   <u>4-Phenoxyproline methyl ester</u>
20   <u>hydrochloride</u>.

           To a cooled solution (ice bath) of N-tert-
Butoxycarbonyl-4-phenoxyproline methyl ester (0.6 g) in
20 ml of ethyl acetate was bubbled anhydrous hydrogen
chloride until saturated. The mixture was warmed to
25   room temperature and stirred for 3 hrs. then
concentrated to give 480 mg of the title compound.

           ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.22 (m,2H), 6.95 (m 1
H), 6.83 (m, 2H), 5.1 (br., 1H), 4.6 (br. m, 1H), 4.06

(br. m, 1H), 3.75 (s, 3H), 3.55 (br. m, 1H), 2.58 (m, 2H).

Step C.   N-Acetyl-tyrosinyl-valinyl-(4-phenoxy)proline methyl ester.

5   N-Acetyl-tyrosinyl-valine (0.524 g, 1.63 mmol) and 4-phenoxyproline methyl ester (0.381 g, 1.48 mmol) were dissolved in 4 ml each of dimethylformamide and dichloromethane and cooled to 0° C. To the cooled solution was added diisopropylethylamine (258 ul, 1.86

10   mmol), HOBT (0.24 g, 1.78 mmol), and EDC (0.37 g, 1.92 mmol) and the reaction was stirred for 18 hrs. The mixture was diluted with 400 ml of ethyl acetate and washed with water, 10% sodium hydrogen sulfate, 10% sodium bicarbonate, and water. The organic layer was

15   concentrated to give a residue that was purified by flash chromatography (SiO_2) eluting with 94:6:1 (CH_2Cl_2:i-PrOH:Pyridine) to afford 360 mg of the title compound.

^{1}H NMR (500 MHz, $CDCl_3$ (existing as rotamers)) δ

20   7.3 (m, 2H), 7.05 (m, 1H), 6.95 (d, 2H), 6.9-6.2 (4 x d, 4H), 5.05 (br. s, 1H), 4.7-3.94 (m,5H), 2.93 (m, 1H), 2.82(m, 1H), 2.65 (m, 1H), 2.2 (m, 1H), 2.05 (m, 1H), 1.95 (s, 3H), 1.86, (m, 1H), 0.98 (d, 3H), 0.88 (d, 3H).

25   Step D.   N-Acetyl-tyrosinyl-valinyl-(4-phenoxy)proline.

Lithium hydroxide (57 mg, 1.37 mmol) was added to a solution of N-Acetyl-tyrosinyl-valinyl-(4-phenoxy)proline methyl ester (360 mg, 0.685 mmol)

30   dissolved in 8 ml of tetrahydrofuran/water (1:1) and

stirred at room temperature for 1 hour. The mixture
was acidified with 10% hydrochloric acid giving a white
precipitate that was collected to give 175 mg of the
title compound.

5   ^{1}H NMR (500 MHz, DMSO-d6) δ 9.2 (br. s, 1H),
8.05-7.95 (m, 2H), 7.3 (m, 1H), 7.0-6.9 (m,4H), 6.65
(d, 2H), 4.42 (m, 1H), 4.35(m, 1H), 4.05-3.95 (m, 2H),
3.3 (br. s, 2H), 2.75 (m, 1H), 2.55-2.38 (m, 2H), 2.2
(m, 1H), 2.0 (m, 1H), 1.7 (s, 3H), 0.95 (d, 3H), 0.85
10   (d, 3H).

Step E. N-[N-Acetyl-tyrosinyl-valinyl-(4-
        phenoxy)prolinyl]-4-amino-5-benzyloxy-2-
        oxotetrahydrofuran.

The title compound was prepared by the method
15   reported for compound H, step A, by reaction of N-
acetyl-tyrosinyl-valinyl-(4-phenoxy)proline and N-
allyloxycarbonyl-4-amino-5-benzyloxytetrahydrofuran.

^{1}H NMR (500 MHz, CDCl$_3$ (existing as a 1:1
diastereomer mixture of the hemiacetal)) δ 7.8-6.3 (m,
20   17H), 5.6 (d, 1H), 5.1-4.15 (m, 5H), 4.15-3.75 (m, 2H),
2.95-2.15 (m, 5H), 2.15-1.95 (m, 1H), 1.9-1.85 (2 x s,
3H), 1.1-0.75 (m, 6H).

Step F.   N-[N-Acetyl-tyrosinyl-valinyl-(4-
           phenoxy)prolinyl]-3-amino-4-oxobutanoic
25   acid.

The title compound was prepared by the
hydrogenolysis procedure reported for compound H,
step D.

^{1}H NMR (500 MHz, CD$_3$OD (existing as a 1:1 diastereomer mixture of the hemiacetal)) δ 7.25 (m, 2H), 7.10-6.85 (m, 5H), 6.65 (d, 2H), 5.1 (br. m, 1H), 4.65-4.05 (m, 5H), 4.0-3.40 (m, 2H), 2.95-2.35 (m, 5H), 2.25 (m, 1H), 2.05 (m, 1H), 1.85 (s, 3H), 1.0 (d, 3H), 0.95 (d, 3H).

K. N-[N-Acetyl-tyrosinyl-valinyl-(4-benzyloxy)prolinyl]-3-amino-4-oxobutanoic acid.

Step A.   N-(N-Allyloxycarbonyl-4-benzyloxyprolinyl)-3-amino-4-oxobutanoic acid tert-butyl ester semicarbazone.

The title compound was prepared by the reaction of N-allyloxycarbonyl-4-benzyloxyproline and 3-amino-4-oxobutanoic acid tert-butyl ester semicarbazone (T.L. Graybill et. al., Abstracts of papers, 206th National Meeting of the American Chemical Society, Abstract MEDI-235. Chicago, IL. (1993)) under similar peptide coupling conditions as reported above (compound H; Step C).

^{1}H NMR (500 MHz, CDCl$_3$) δ 9.05 (br. s, 1H), 7.85 (br. m, 1H), 7.4-7.2 (m, 5H), 7.15 (br. s, 1H), 6.55 (br. s, 1H), 5.9 (m, 1H), 5.1-4.9 (br. m, 2H), 4.65-4.4 (m, 4H), 4.2 (br. m, 1H), 3.75-3.5 (m, 2H), 2.75-2.55 (m, 2H), 2.5 (br. m, 1H), 2.25 (br. m, 1H) 1.4 (s, 9H).

Step B.   N-(N-Acetyl-tyrosinyl-valinyl-(4-benzyloxyprolinyl))-3-amino-4oxobutanoic acid tert-butyl ester semicarbazone.

The title compound was prepared by reaction of N-acetyl-tyrosinyl-valine and N-(N-allyloxycarbonyl-4-

benzyloxyprolinyl)-3-amino-4-oxobutanoic acid tert-butyl ester semicarbazone by reaction conditions reported for compound $\underline{H}$, step A.

^{1}H NMR (500MHz, CD$_3$OD) δ 7.35-7.2 (m, 6H), 7.0 (d, 2H), 6.65(d, 2H), 4.85 (m, 1H), 4.6-4.45 (m, 4H), 4.3 (br. m, 1H), 4.15 (m, 1H), 3.7 (m, 1H), 2.95 (m, IH), 2.75-2.6 (m, 3H), 2.35 (m, 1H), 2.1 (m, 1H), 1.9 (s, 3H), 1.4 (s, 9H), 0.95 (d, 3H), 0.90 (s, 3H).

Step C. N-(N-Acetyl-tyrosinyl-valinyl-(4-benzyloxyprolinyl))-3-amino-4oxobutanoic acid.

N-(N-Acetyl-tyrosinyl-valinyl-(4-benzyloxyprolinyl))-3-amino-4-oxobutanoic acid tert-butyl ester semicarbazone (270 mg) was dissolved into 10 ml of 25% trifluoroacetic acid in dichloromethane and stirred at room temperature for 3 hours. The mixture was concentrated to give a solid residue. The residue was dissolved into a 10 ml mixture of methanol:acetic acid:37% formaldehyde (3:1:1) and stirred at room temperature for 1 hour. The mixture was concentrated and the resulting residue purified by flash chromatography (SiO$_2$) eluting with dichloromethane/methanol/formic acid (100:5:0.5) to give 37 mg of the title compound.

^{1}H NMR (500 MHz, CD$_3$OD (existing as a 1:1 mixture of diastereomers of the hemiacetal)) δ 7.4-7.25 (m, 5H), 7.0 (d, 2H), 6.65 (d, 2H), 4.65-4.05 (m, 7H), 3.75-3.4 (m, 2H), 3.05-2.3 (m, 5H), 2.2-1.95 (m, 2H), 1.90 (s, 3H), 1.0 (d, 3H), 0.95 (d, 3H).

Example 4

We obtained inhibition constants (K_i) and IC_{50} values for several compounds of this invention using enzyme assays with UV-visible substrate and cell assays as described in Example 2. The following K_i and IC_{50} values were determined for compounds 7a, 7b, 20a-d, 21c-f, 22e, 25, 28, 33a-c, 36a, 36b, 39, 43, 47a, 47b, 54a-l, 63, 69a, 69b, 84a and 84b using the indicated assays. Corresponding lettered compound designations are indicated parenthetically. The compound structures are shown in Examples 2 and 5.

	Assay	
Compound	UV-visible K_i (μM)	Cell IC_{50} (μM)
7a	35	
7b	1.2	
20a (= E)	3.2	
20b	0.85	16.4
20c (= N)	0.95	
20d	0.1	6.2
21c	0.64	
21d	0.24	4.8
21e	0.22	2.9
21f	0.17	2.9
22e	0.19	
25	6.2	
28	12.0	
33a (= A)	5.5	25.0
33b (= C)	10.0	>30.0
33c (= B)	8.6	20.0
36a (= D)	4.7	
36b	0.8	17.0
39	2.5	
43	20.0	

	47a		0.019	2.1
	47b		0.027	1.8
	54a	(= F)	0.15	2.7
	54b	(= M)	0.15	9.1
5	54c		1.2	>19.0
	54d		1.0	
	54e		3.5	
	54f		0.9	
	54g	(= G)	4.8	>20.0
10	54h		0.97	
	54i		0.054	2.4
	54j		0.28	
	54k		0.085	
	54l		0.215	7.0
15	63	(= Q)	0.85	4.1
	69a	(= R)	0.011	0.735
	69b	(= S)	0.050	0.745
	84a	(= V)	0.100	3.3
	84b	(= W)	0.019	0.50

Example 5

Compounds of Example 4 were synthesized as follows:

1   **2**   **3**

4   **5**

6

7
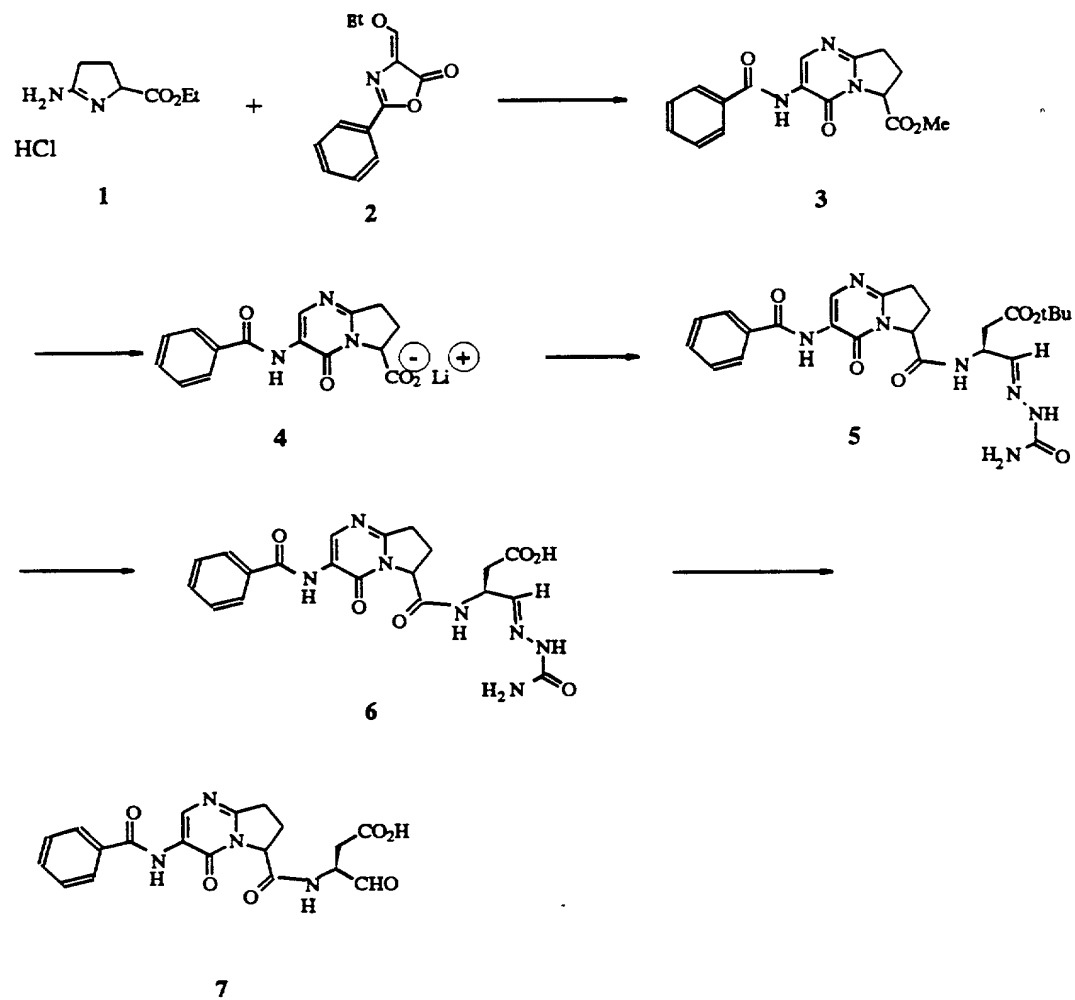
3-Benzoylamino-4-oxo-4,6,7,8-tetrahydro-pyrrolo[1,2-a]pyrimidine-6-carboxylic acid methyl ester (3). A mixture of (4S)-2-amino-1-pyrroline-5-carboxylic acid ethyl ester hydrochloride (1, 0.44g, 2.38mmol; prepared in an analogous fashion as the methyl ester as described by Lee and Lown, _J. Org. Chem._, 52, 5717-21 (1987)); 4-ethoxymethylene-2-phenyl-2-oxazolin-5-one (2, 0.50g, 2.31mmol) and sodium methoxide (0.12g, 2.22mmol) in ethanol (10ml) was refluxed for 2h. The reaction was allowed to cool to room temperature and concentrated in vacuo. The residue was suspended in water and 1N sulfuric acid was added until pH 1 was reached. The aqueous mixture was extracted with dichloromethane, the organic layer was separated and concentrated in vacuo to yield 0.6g of a orange solid. Chromatography (flash, SiO_2, 60% ethyl acetate/hexane increased to 100% ethyl acetate stepwise gradient, then 10% methanol/dichloromethane) to give 0.5g of an orange solid. A mixture of the orange solid and potassium cyanide (0.03g, 0.5mmol) in methanol (10ml) was refluxed overnight. The cooled reaction was concentrated in vacuo to give a yellow solid. Chromatography (flash, SiO_2, 40% ethyl acetate/hexane to 100% ethyl acetate stepwise gradient) afforded 0.22g (31.6%) of the title compound: ^1H NMR (d_6-DMSO) δ 2.25 (m, 1H), 2.65 (m, 1H), 3.15 (m, 2H), 3.75 (s, 3H), 5.15 (dd, 1H), 7.5 (t, 2H), 7.6 (t, 1H), 7.95 (d, 2H), 8.6 (s, 1H), 9.5 (s, 1H).

(3S)-[(3-benzoylamino-4-oxo-4,6,7,8-tetrahydro-pyrrolo[1,2-a]pyrimidine-6-carbonyl)-amino]-4-oxo-butanoic acid tert-butyl ester semicarbazone (5a and 5b). A mixture of 3-benzoylamino-4-oxo-4,6,7,8-tetrahydro-pyrrolo[1,2-a]pyrimidine-6-carboxylic acid ethyl ester (3, 0.22g 0.70mmol) and lithium hydroxide

hydrate (0.032g, 0.76mmol) in methanol (5ml) and
tetrahydrofuran (5ml) and was stirred 18h at room
temperature. The reaction was concentrated to give
3-benzoylamino-4-oxo-4,6,7,8-tetrahydro-pyrrolo[1,2-
5   a]pryrimidine-6-carboxylic acid lithium salt (4) as a
white solid. This was used without further
purification in the subsequent reaction.

A 0°C mixture of (3S)-amino-4-oxo-butanoic acid
tert-butyl ester semicarbazone (0.163g, 0.71mmol;
10   Graybill et al., Int. J. Protein Res., 44, pp. 173-82
(1994)) and 3-benzoylamino-4-oxo-4,6,7,8-tetrahydro-
pyrrolo[1,2-a]pyrimidine-6-carboxylic acid lithium salt
(4) in dimethylformamide (5ml) and dichloromethane
(5ml) was treated with hydroxybenzotriazole (0.104g,
15   0.77mmol) and 1-(3-dimethylaminopropyl)-3-ethyl
carbodiimide hydrogen chloride (0.148g. 0.37mmol). The
reaction was allowed to·warm to room temperature and
stirred 18hr. The reaction was poured onto water
(50ml) and extracted with ethyl acetate (2 x 50mL).
20   The combined organic layers were washed with aqueous 1M
sodium hydrogen sulfate solution, dilute aqueous sodium
hydrogen carbonate (50mL) and saturated aqueous sodium
chloride. The organic layer was concentrated in vacuo
to yield 0.43g of a yellow solid. Chromatography
25   (flash, SiO_2, ammonium hydroxide/methanol/di-
chloromethane (1:1:99 to 1:10:90 stepwise gradient))
gave 0.11g (30.9%) of the higher Rf diastereomer (5a):
^{1}H NMR (CD$_3$OD) δ 1.45 (s, 9H), 2.29-2.35 (m, 1H), 2.6-
2.7 (m, 2H), 2.8 (dd, 1H), 3.1-3.15 (m, 1H), 3.2-3.3
30   (m, 1H), 4.9-4.95 (m, 1H), 5.2 (dd, 1H), 7.25 (d, 1H),
7.5-7.55 (m, 2H), 7.55-7.6 (m, 1H), 7.95 (d, 2H), 8.9
(s, 1H) and 0.11g (30.9%) of the lower Rf diastereomer
(5b): ^{1}H NMR (CD$_3$OD) δ 1.45 (s,9H), 2.3-2.4 (m, 1H),
2.6-2.7 (m, 1H), 2.7-2.8 (m, 2H), 3.1-3.15 (m, 1H),
35   3.2-3.3 (m, 1H), 4.85-4.95 (m, 1H), 5.15 (dd, 1H), 7.25

(d, 1H), 7.55 (t, 2H), 7.6 (t, 1H), 7.95 (d, 2H), 8.9 (s, 1H). Diastereomer **5a** and diastereomer **5b** were taken on separately.

(3S)-[(3-benzoylamino-4-oxo-4,6,7,8-tetrahydro-pyrrolo[1,2-a]pyrimidine-6-carbonyl)-amino]-4-oxo-butanoic acid (7a). A suspension of (3S)-[(3-benzoylamino-4-oxo-4,6,7,8-tetrahydro-pyrrolo[1,2-a]pyrimidine-6-carbonyl)-amino]-4-oxo-butanoic acid tert-butyl ester semicarbazone (**5a**, 0.11g, 0.22mmol) in dichloromethane (7.5ml) and trifluoroacetic acid (2.5ml) was stirred for 5h. The reaction was concentrated in vacuo, the residue was taken up in dichloromethane, concentrated in vacuo, suspended in toluene and concentrated in vacuo to give 0.07 g of (3S)-[(3-benzoylamino-4-oxo-4,6,7,8-tetrahydro-pyrrolo[1,2-a]pyrimidine-6-carbonyl)-amino]-4-oxo-butanoic acid semicarbazone (**6a**) as a white solid. The solid was suspended in a mixture of 37% aqueous formaldehyde/acetic acid/methanol (1:1:5) and stirred at room temperature for 18hr. The reaction was concentrated in vacuo, the residue was suspended in acetonitrile and concentrated in vacuo to give 0.1g of a white solid. Chromatography (HPLC, reverse phase C18, 1% to 75% acetonitrile/water (buffered with 0.1% trifluoroacetic acid) gradient elution) to give 0.05g (60%) of **7a** as a white solid: RT = 7.9 min (HPLC, C18 reverse phase, 1 to 100% acetonitrile/water (0.1% trifluoroacetic acid buffer); 20 min gradient elution); ^{1}H NMR (CD$_3$OD (existing as a 1:1 mixture of anomers of the hemi-acyloxy acetal form)) δ 2.25-2.4 (m, 1H), 2.45-2.8 (m, 4H), 3.05-3.15 (m, 1H), 4.25-4.35 (m, 1H), 4.55-4.6 (m, 1H), 5.1-5.2 (m, 1H), 7.45-7.65 (m, 3H), 7.9-8.0 (m, 2H), 8.9 (s, 1H).

(3S)-[(3-benzoylamino-4-oxo-4,6,7,8-tetrahydro-pyrrolo[1,2-a]pyrimidine-6-carbonyl)-amino]-4-oxo-butanoic acid (7b) was prepared as described for diastereomer **7a** to give 0.03g (35%) of **7b** as a white solid: RT = 8.1 min (HPLC, C18 reverse phase, 1 to 100% acetonitrile/water (0.1% trifluoroacetic acid buffer); 20 min gradient elution); ^{1}H NMR (d_6-DMSO (existing as a 1:1 mixture of anomers of the hemi-acyloxy acetal form)) δ 2.1-2.2 (m, 1H), 2.4 (d, 1H), 2.7-2.8 (m, 1H), 3.0-3.2 (m, 3H), 5.0 (dd, 1H), 5.1-5.2 (m, 1H), 5.5 (s, 1H), 5.7-5.8 (m, 1H), 7.55 (t, 2H), 7.67 (t, 1H), 7.95 (d, 2H), 8.55 (s, 1H), 9.0-9.15 (m, 1H), 9.4-9.5 (m, 1H).

13

14

15

16

17

18

19

20

21

22

a   R = H
b   R = PhCH$_2$
c   R = Ph(CH$_2$)$_2$
d   R = Ph(CH$_2$)$_3$
e   R = 4MeO-Ph(CH$_2$)$_3$
f   R = 4HO-Ph(CH$_2$)$_3$

Imidazole-2-carboxylic acids **13** were prepared using
modifications of described procedures (Yamanaka et al.,
Chem. Pharm. Bull., 31, pp. 4549-53 (1983)); Suzuki et
al., J. Org. Chem., 38, pp. 3571-75 (1973)); and Oliver
et al. (J. Org. Chem., 38, pp. 1437-38 (1973)).

Imidazole-2-carboxylic acid (13a) was prepared according to Curtis and Brown, J. Org. Chem., 45, pp. 4038-40 (1980).

4-Benzylimidazole-2-carboxylic acid (13b), was isolated
5   as an off-white solid: mp. 153-155°C;   IR (KBr) 3026-2624, 1630, 1515, 1498, 1438, 1405; ^{1}H NMR(d_6-DMSO) δ 7.31 (5H, m), 7.14 (1H, s), 3.95 (2H, s).

4-(2-Phenylethyl)imidazole-2-carboxylic acid (13c), was isolated as a pale yellow solid: mp. 151-153°C;   IR
10   (KBr) 3054-2617, 1637, 1497, 1376; ^{1}H NMR(d_6-DMSO) δ 7.27 (5H, m), 7.11 (1H, s), 2.92 (4H, s).

4-(3-Phenylpropyl)imidazole-2-carboxylic acid (13d), was isolated as a pale yellow solid: mp. 148-150°C; IR (KBr) 3020-2615, 1636, 1509, 1498, 1383; ^{1}H NMR(d_6-
15   DMSO) δ 7.35-7.22 (5H, m), 7.01 (1H, s), 2.62 (4H, m), 1.94 (2H, m).

4-[3-(4-Methoxyphenyl)propyl]imidazole-2-carboxylic acid (13e), was isolated as a white crystalline solid: mp. 155-156°C (decomp.); IR (KBr) 3300-2300, 1633,
20   1513, 1376, 1244; ^{1}H NMR(d_6-DMSO) δ 9.50-7.50 (2H, bs), 7.15 (1H, s), 7.11 (2H, d, J=8.5), 6.84 (2H, d, J=8.5), 3.71 (3H, s), 2.60-2.50 (4H, m), 1.86 (2H, m). Anal. Calcd for $C_{14}H_{16}N_2O_3$:   C, 64.60; H, 6.20; N, 10.76. Found: C, 64.45; H, 6.21; N, 10.70.

25   **4-[3-(4-Hydroxyphenyl)propyl]imidazole-2-carboxylic acid (13f)**. A solution of the ethyl ester of **13e** (1.15g, 4.0mmol) in dry dichloromethane (50ml) was treated with boron tribromide (16ml, 1.0M solution in CH_2Cl_2, 16.0mmol) at 0°C. After 15min at 0°C, the

mixture was warmed to 25°C and stirred for 16h. The reaction mixture was cooled in an ice bath and quenched with a dropwise addition of water (20ml). The resulting mixture was briefly stirred at 25°C then filtered. The filtrate was carefully neutralised by the addition of solid $NaHCO_3$ to afford **13f** (700mg, 71%) as a white solid: m.p. 186-187°C (decomp.) (recrystallised from MeOH); IR (KBr) 3500-2400, 2935, 1640, 1516, 1396, 1232; ^1H NMR(d_6-DMSO) δ 9.83 (3H, bs), 7.16 (1H, s), 6.98 (2H, d, J=8.2), 6.66 (2H, d, J=8.2), 2.60-2.40 (4H, m), 1.84 (2H, m). Anal. Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 62.96; H, 5.70; N, 11.27.

(2R,S, 3S) N^2-Tert-butoxycarbonyl-N-(tetrahydro-2-benzyloxy-5-oxo-3-furanyl)-L-alaninamide (14). Tri-n-butyl tin hydride (4.0ml, 14.9mmol) was added dropwise to a solution of (2R,S, 3S) 3-(N-allyloxycarbonyl) amino-2-benzyloxy-5-oxotetrahydrofuran (Chapman, _Biorg. Med. Chem. Lett_., 2, pp. 613-18 (1992); (2.91g, 10mmol)), N-tert-butoxycarbonyl-L-alanine (2.08g, 11mmol) and bis(triphenylphosphine)palladium (II) chloride (150mg) in dichloromethane (75ml) until the colour of the solution turned dark orange. Hydroxybenzotriazole (2.70g, 20mmol) was added, and the mixture cooled to 0°C. 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride (2.30g, 12mmol) was added then the mixture was allowed to warm slowly to room temperature during 4h. The mixture was diluted with ethyl acetate (250ml) and washed with 1N hydrochloric acid (3 x 150ml), saturated aqueous sodium bicarbonate (3 x 150ml) and brine (2 x 150ml), then dried ($MgSO_4$), filtered and concentrated. The crude product was purified by column chromatography (50-70% ethyl acetate/hexane) to afford 3.17g (84%) of a

mixture of diastereomers. Recrystallization (ethyl acetate-hexane) gave colorless crystals: mp. 132-145°C; IR (KBr) 3357, 3345, 1781, 1688, 1661, 1535, 1517, 1165; ^{1}H NMR(d_6-DMSO) δ 8.49 (d, J = 6.8), 8.23 (d, J = 7.4), 7.40 (5H, m), 7.01 (1H, m), 5.68 (d, J = 5.0), 4.75 (m), 4.31 (m), 3.97 (1H, m), 2.82 (m), 3.11 (m), 2.82 (m), 2.59 (m), 2.45 (m), 1.40 (9H, s), 1.20 (d, J = 7.2), 1.16 (d, J = 7.2). Anal. Calcd for $C_{19}H_{26}N_2O_6$: C, 60.31; H, 6.92; N, 7.40. Found C, 60.30; H, 6.91; N, 7.38.

(2R,S, 3S) tert-Butoxycarbonyl-N-(tetrahydro-2-benzyloxy-5-oxo-3-furanyl)-L-prolinamide (15), was prepared by the method described for **14** to afford 1.64g (81%) of a colorless glass. IR (KBr) 3317, 2978, 1797, 1697, 1670, 1546, 1400, 1366, 1164, 1121; ^{1}H NMR(CDCl$_3$) δ 7.68 (1H, brm), 7.35 (5H, m); 5.53 (d, J=5.2), 5.43 (s), 4.93-4.61 (m), 4.44 (m), 4.25 (brm), 3.39 (2H, brm), 3.10-2.81 (1H, m), 2.44 (1H, m), 2.32 (brm), 1.88 (brm), 1.67 (brm), 1.42 (9H, s).

(2R,S, 3S) N-(N-tert-Butoxycarbonyl-(4(R)-phenoxy-L-prolinyl)-3-amino-2-benzyloxy-5-oxotetrahydrofuran (16) was prepared by the method described for **14** to afford 530mg (84%) of a colorless amorphous solid: ^{1}H NMR (CDCl$_3$) δ 7.65 (1H, m), 7.4-7.2 (7 H, m), 6.95 (1H, m), 6.85 (1H, m), 5.55(1H, d), 4.95 (1H, d), 4.8-4.7 (1H, brm), 4.65 (1H, d), 4.55-4.45 (1H, brm), 4.4-4.3 (0.5H, brm), 3.95-3.85 (0.5H, brm), 3.75-3.58 (2H, m), 2.95-2.8 (1H, m), 2.7-2.55 (1H, m), 2.54-2.4 (1H, m), 2.35-2.2 (1H, m), 1.4 (9H,s).

(2R,S, 3S) N^2-[4-(3-Phenylpropyl)imidazole-2-carbonyl]-N-(tetrahydro-2-benzyloxy-5-oxo-3-furanyl)-L-alaninamide (17d). Trifluoroacetic acid (7ml) was

added to a solution of (2R,S, 3S) N²-tert-
butoxycarbonyl-N-(tetrahydro-2-benzyloxy-5-oxo-3-
furanyl)-L-alaninamide **(14)** (1.00g, 2.64mmol) in
dichloromethane (7ml) at 0°C. The mixture was stirred
at 0°C for 75 min. The mixture was concentrated, and
the residue treated with diethyl ether then the ether
was removed under vacuum. This procedure was repeated
twice to yield a pale yellow glass. The solid was
dissolved in DMF (20ml). Diisopropylethylamine
(1.38ml, 7.92mmol) followed by 4-(3-phenylpropyl)
imidazole-2-carboxylic acid **(13d)** (0.67g, 290mmol), 1-
(3-dimethylaminopropyl)-3-ethyl carbodiimide
hydrochloride (0.56g, 2.90mmol) and
hydroxybenzotriazole (0.71g, 5.28mmol) were then added
to this solution. The mixture was stirred at room
temperature for 20h then poured into brine. The
mixture was extracted with ethyl acetate (3 x 50ml).
The combined organic extracts were washed with
saturated aqueous sodium bicarbonate (2 x 100ml) then
brine (2 x 100ml), dried (MgSO₄), filtered and
concentrated. The residue was purified by column
chromatography (ethyl acetate) to afford 0.99g (76%) of
17d as a mixture of diastereomers: IR (KBr) 3293,
3064, 2937, 1793, 1650, 1530, 1451, 1446, 1119; ¹H NMR
(CDCl₃) δ 7.96 (brm), 7.62 (brd), 7.36-7.10 (10H, m),
6.88 (s), 6.86 (s), 5.53 (d, J=5.2), 5.48 (s), 4.87-
4.52 (4H, m), 3.11-2.38 (2H, m), 2.65 (4H, m), 1.99
(2H, m), 1.47 (d, J=6.9), 1.46 (d, J=7.0).

The following compounds were prepared in a similar
manner:

**(2R,S, 3S) N²-(Imidazole-2-carbonyl)-N-(tetrahydro-2-
benzyloxy-5-oxo-3-furanyl)-L-alaninamide (17a),** was

isolated (74%) as a pale yellow solid: IR (KBr) 3289, 3056, 2937, 1793, 1664, 1642, 1528, 1453, 1440, 1124; ^{1}H NMR (d$_6$-DMSO) δ 13.13 (1H, brs), 8.67 (d, J=7.0), 8.48 (d, J=7.8), 8.29 (d, J=6.8), 8.25 (d, J=7.6), 7.40-7.34 (6H, m), 7.11 (1H, s), 5.69 (d, J=5.0), 5.49 (d, J=0.8), 4.85-4.31 (4H, m), 3.19-2.42 (2H, m), 1.38 (d, J=7.4), 1.34 (d, J=7.4).

(2R,S, 3S) N^2-(4-Benzylimidazole-2-carbonyl)-N-(tetrahydro-2-benzyloxy-5-oxo-3-furanyl)-L-alaninamide (17b), was isolated (75%) as a pale yellow glass: IR (KBr) 3294, 3031, 2937, 1792, 1650, 1530, 1453, 1444, 1119; ^{1}H NMR(CDCl$_3$) δ 7.99 (brm), 7.75 (brd), 7.36-7.11 (10H, m), 6.81 (1H, s), 5.51, 5.45 (d, s, J=5.3), 4.85-4.47 (4H, m), 3.95 (2H, s), 3.04-2.72 (1H, m), 2.48-2.35 (1H, m), 1.44 (d, J=6.9), 1.43 (d, J=7.1).

(2R,S, 3S) N^2-[4-(2-Phenylethyl)imidazole-2-carbonyl]-N-(tetrahydro-2-benzyloxy-5-oxo-3-furanyl)-L-alaninamide (17c), was isolated (79%) as a pale yellow glass: IR (KBr) 3292, 3029, 2936, 1793, 1650, 1530, 1453, 1444, 1119; ^{1}H NMR(CDCl$_3$) δ 8.06 (brm), 7.70 (brs), 7.39-7.15 (10H, m), 6.82 (s), 6.81 (s), 5.53 (d, J=5.2), 5.48 (s), 4.87-4.53 (4H, m), 2.95 (4H, m), 3.11-2.37 (2H, m), 1.48 (d, J=5.6), 1.45 (d, J=6.7).

(2R,S, 3S) 1-[4-(2-Phenylethyl)imidazole-2-carbonyl]-N-(tetrahydro-2-benzyloxy-5-oxo-3-furanyl)-L-prolinamide (18c), was isolated (79%) as a pale yellow glass: IR (CH$_2$Cl$_2$) 3422, 2959, 1795, 1685, 1611, 1497, 1116; ^{1}H NMR(d$_6$-DMSO) δ 12.78-12.59 (1H, m), 8.61-8.34 (1H, m), 7.39-7.22 (10H, m), 6.99-6.61 (1H, m), 5.71-5.26 (1H, m), 4.85-4.02 (4H, m), 3.63 (1H, m), 3.18-1.74 (11H, m).

(2*R*,*S*, 3*S*) 1-[4-(3-Phenylpropyl)imidazole-2-carbonyl]-
N-(tetrahydro-2-benzyl-oxy-5-oxo-3-furanyl)-L-
prolinamide (18d), was isolated (87%) as a colorless
glass: IR (CH$_2$Cl$_2$) 3422, 3214, 2945, 1794, 1685, 1604,
5   1496, 1117; ^{1}H NMR(d$_6$-DMSO) δ 12.71 (1H, brm), 8.61-
8.34 (1H, m), 7.45-7.18 (10H, m), 7.05-6.64 (1H, m),
5.70-5.28 (1H, m), 4.85-4.02 (4H, m), 3.62 (1H, m)
3.18-1.71 (13H, m).

(2*R*,*S*, 3*S*) 1-{4-[3-(4-Methoxyphenyl)propyl]imidazole-2-
10 carbonyl}-N-(tetra-hydro-2-benzyloxy-5-oxo-3-furanyl)-
L-prolinamide (18e), was isolated (72%) as a white
glassy solid: mp. 62-65°C; IR (KBr) 3213, 2937, 1793,
1680, 1606, 1606, 1512, 1245; ^{1}H NMR(d$_6$-DMSO) δ 12.71,
12.67, 12.58 (1H, 3 x bs), 8.60-8.30 (1H, m), 7.40-7.20
15 (5H, m), 7.15-6.55 (5H, m), 5.66-5.20 (1H, m), 4.81-
4.59 (2H, m), 4.55-4.05 (2H, m), 3.71 (3H, s), 3.65-
3.45 (1H, m), 3.15-1.50 (13H, m). FABSMS m/e 547 (M$^+$,
100%), 439, 412, 340, 312, 243, 177, 154.

(2*R*,*S*, 3*S*) 1-{4-[3-(4-Hydroxyphenyl)propyl]imidazole-2-
20 carbonyl}-N-(tetra-hydro-2-benzyloxy-5-oxo-3-furanyl)-
L-prolinamide (18f), was isolated (70%) as a light
yellow glassy solid: mp. 86-90°C; IR (KBr) 3298, 1790,
1669, 1606, 1515, 1242; ^{1}H NMR(d$_6$-DMSO) δ 12.66, 12.56
(1H, 2 x bs), 9.14 (1H, s), 8.57-8.30 (1H, m), 7.36-
25 7.30 (5H, m), 7.02-6.83 (3H, m), 6.70-6.57 (2H, m),
5.65-5.28 (1H, m), 4.80-4.49 (2H, m), 4.50-4.05 (2H,
m), 3.65-3.45 (1H, m), 3.15-1.55 (13H, m). FABMS m/e
533 (M$^+$, 100%), 425, 298, 229, 176, 154.

1-{5-[3-(4-Methoxyphenyl)propyl]-1H-imidazole-2-
30 carbonyl}-4(R)-phenoxypyrrolidine-2(S)-carbonyl-
(tetrahydro-2(*R*,*S*)-benzyloxy-5-oxofuran-3(S)-yl)amide
(19e) was isolated (77%) as a clear colorless amorphous

solid. ^{1}H NMR (CDCl$_3$) δ 9.95-9.75 (1H, m), 7.95 (1H, brs), 7.40-7.2 (7H, m), 7.2-6.78 (7H, m), 5.65-5.6 (1H, m), 5.55-5.45 (1H, m), 5.3-5.2 (1H,m), 5.15-5.0 (1H, m), 4.95-4.75 (1H, m), 4.7-4.6 (1H, m), 4.5-4.4 (1H, m), 4.35-4.4.25 (1H, m), 3.8 (3H, s), 3.05-1.75 (10H, m).

(3*S*) 3-{N-[4-(3-Phenylpropyl)imidazole-2-carbonyl]-L-alaninyl}amino-4-oxo-butanoic acid (20d). A mixture of (2*R*,*S*, 3*S*) N^2-[4-(3-Phenylpropyl)imidazole-2-carbonyl]-N-(tetrahydro-2-benzyloxy-5-oxo-3-furanyl)-L-alaninamide (0.93g, 1.90mmol) and 10% palladium on activated carbon (0.93g) in methanol (100ml) was stirred under a hydrogen atmosphere for 5h. The resulting mixture was filtered and concentrated to yield a colorless glass. Recrystallization from methanol-diethyl ether afforded 401mg (53%) of **20d** as a colorless solid: mp. 94-96°C; $[\alpha]_D^{27}$ +16.4° (c 0.5, MeOH); IR (KBr) 3300, 3287, 1786, 1732, 1659, 1651, 1532, 1451; ^{1}H NMR(CD$_3$OD) δ 7.19 (5H, m), 6.91 (1H, s), 4.60-4.46 (2H, m), 4.27 (1H, m), 2.63 (4H, m), 2.75-2.40 (2H, m), 1.96 (2H, m), 1.44 (3H, d, *J*=7.0).

The following compounds were prepared in a similar manner:

(3*S*) 3-[N-(Imidazole-2-carbonyl)-L-alaninyl]amino-4-oxobutanoic acid (20a; E), was isolated (83%) as a colorless solid: mp. 115°C; $[\alpha]_D^{25}$ +4.4° (c 0.5, MeOH); IR (KBr) 3303, 1782, 1658, 1650, 1563, 1521, 1454; 1H NMR(CD$_3$OD) δ 7.18 (2H, s), 4.55 (2H, m), 4.27 (1H, m), 2.56 (2H, m), 1.45 (d, *J*=7.1), 1.44 (d, *J*=7.0).

(3*S*) 3-[N-(4-Benzylimidazole-2-carbonyl)-L-alaninyl]amino-4-oxobutanoic acid (20b), was isolated (56%) as a colorless solid: mp. 113-115°C; $[\alpha]_D^{29}$ +18.2°

25

(c 0.5 MeOH). IR (KBr) 3301, 3288, 1783, 1727, 1650, 1531, 1452; ^{1}H NMR(CD$_3$OD) δ 7.25 (5H, m), 6.90 (1H, s), 4.59-4.45 (2H, m), 4.26 (1H, m), 3.95 (2H, s), 2.74-2.39 (2H, m), 1.42 (3H, d, J=7.0). Anal. Calcd for

5   C$_{18}$H$_{20}$O$_4$O$_5$: C, 56.69; H, 5.55; N, 14.69. Found: C, 57.06; H, 5.54; N, 14.41.

(3S) 3-{N-[4-(2-Phenylethyl)imidazole-2-carbonyl]-L-alaninyl}amino-4-oxobutanoic acid (20c; N), was isolated (53%) as a colorless solid: mp. 102-104°C;

10   [α]$_D$^{27} +13.7° (c 0.5, MeOH); IR (KBr) 3299, 3289, 1785, 1732, 1650, 1531, 1452; ^{1}H NMR(CD$_3$OD) δ 7.20 (5H, m), 6.82 (1H, s), 4.60-4.46 (2H, m), 4.29 (1H, m), 2.92 (4H, s), 2.76-2.41 (2H, m), 1.44 (3H, 2 x d, J=7.1). Anal. Calcd for C$_{19}$H$_{22}$N$_4$O$_5$ H$_2$O: C, 56.43; H, 5.98; N,

15   13.85. Found: C, 56.65; H, 5.84; N, 13.91.

(3S) 3{N-[4-(2-Phenylethyl)imidazole-2-carbonyl]-L-prolinyl}amino-4-oxobutanoic acid (21c), was isolated (85%) as a colorless glass: mp. 101-103°C (methanol-diethyl ether); [α]$_D$^{27} -63.8° (c 0.25, MeOH); IR (KBr)

20   3275, 1784, 1728, 1664, 1606, 1498, 1429; ^{1}H NMR(CD$_3$OD) δ 7.24 (5H, m), 6.83 (s), 6.79 (s), 4.58-4.14 (3H, m), 3.69 (1H, m), 2.93 (4H, brs), 2.75-1.99 (6H, m). Anal. Calcd for C$_{21}$H$_{24}$N$_4$O$_5$ H$_2$O: C, 58.60; H, 6.09; N, 13.02. Found: C, 58.34; H, 5.96; N, 12.67.

25   **(3S) 3-{N-[4-(3-Phenylpropyl)imidazole-2-carbonyl]-L-prolinyl}amino-4-oxo-butanoic acid (21d)**, was isolated(81%) as a colorless glass: mp. 91-94°C; (methanol-diethyl ether); [α]$_D$^{25} -68° (c 0.25, MeOH); IR (KBr) 3277, 2939, 1784, 1727, 1662, 1606, 1498, 1429;

30   ^{1}H NMR(CD$_3$OD) δ 7.29-7.16 (5H, m), 6.92 (s), 6.86 (s), 4.58-4.16 (3H, m), 3.71 (1H, m), 2.75-1.92 (13H, m). Anal. Calcd for C$_{22}$H$_{26}$N$_4$O$_5$ H$_2$O: C, 59.45; H, 6.35; N,

12.60. Found: C, 59.75; H, 6.21; N, 12.41.

(3S) 3-{N-[4-[3-(4-Methoxyphenyl)propyl]imidazole-2-carbonyl]-L-prolinyl}amino-4-oxobutanoic acid (21e),
was isolated (65%) as a white glassy solid: mp. 101-
105°C; [α]$_D^{23}$ -60.6 (c 0.05, MeOH); IR (KBr) 3231, 1784,
1726, 1611, 1512, 1245; ^{1}H NMR(CD$_3$OD) δ 7.09 (2H, d,
J=8.6), 6.92, 6.85 (1H, 2 x s), 6.81 (2H, d, J=8.6),
5.45-5.30 (1H, m), 4.64-4.46 (1H, m), 4.28-4.10 (2H,
m), 3.75 (3H, s), 3.74-3.66 (1H, m), 2.67-1.84 (13H,
m). Anal. Calcd for C$_{23}$H$_{28}$N$_4$O$_6$ H$_2$O: C, 58.22; H, 6.37; N,
11.81. Found: C, 58.39; H, 6.34; N, 11.45; FABMS m/e
457 (M$^+$), 405, 312, 243, 215, 176, 154 (100%).

(3S) 3-{N-[4-[3-(4-Hydroxyphenyl)propyl]imidazole-2-carbonyl]-L-prolinyl}amino-4-oxobutanoic acid (21f),
was isolated (43%) as a white glassy solid: mp. 114-
118°C; [α]$_D^{25}$ -55.7° (c 0.05, MeOH); IR (KBr) 3288,
2935, 1780, 1715, 1662, 1610, 1515, 1441; ^{1}H NMR(CD$_3$OD)
δ 6.99 (2H, d, J=8.5), 6.91, 6.85 (1H, 2 x s), 6.68
(2H, d, J=8.5), 5.45-5.30 (1H, m), 4.60-4.47 (1H, m),
4.30-4.10 (2H, m), 3.80-3.55 (1H, m), 2.70-1.80 (13H,
m). Anal. Calcd for C$_{22}$H$_{26}$N$_4$O$_6$ H$_2$O: C, 57.38; H, 6.13; N,
12.17. Found: C, 57.68; H, 6.25; N, 11.66. FABMS m/e
443 (M$^+$), 298, 229, 154 (100%).

3(S)-[(1-{5-[3-(4-Methoxyphenyl)propyl]-1H-imidazole-2-carbonyl}-4(R)-phenoxy pyrrolidine-2(S)-carbonyl)amino]-4-oxobutanoic acid (22e) was isolated
(43%) as a beige solid: ^{1}H NMR (CD$_3$OD) δ 7.35-7.2
(3H,m), 7.15-7.0 (2H,m), 6.98-6.85 (3H, m), 6.83-6.77
(2H,d), 5.4-5.1 (1H,m), 4.65-4.5 (1H,m), 4.35-4.2
(2H,m), 4.15-3.90 (1H,m), 3.78 (3H, s), 3.62-3.48 (1H,
m), 2.78-2.25 (8H, m), 2.02-1.9 (2H,m).
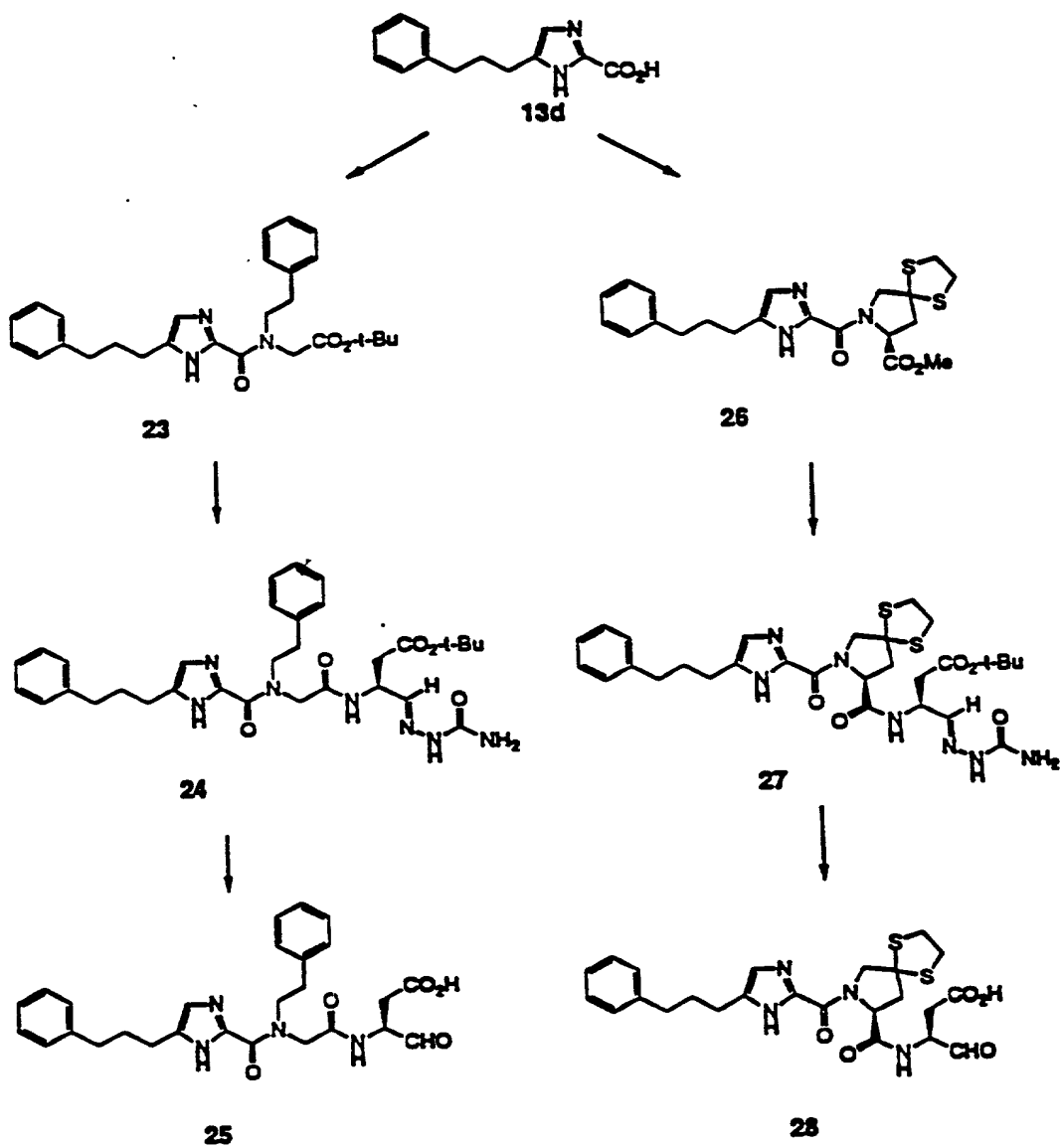
{Phenethyl-[5-(3-propyl)-1H-imidazole-2-carbonyl]amino}acetic acid tert-butyl ester (23).
A 0°C solution of 4-(3-phenylpropyl)-imidazole-2-carboxylic (13d) (150mg, 0.65mmol) and N-(2-phenethyl)glycine tert-butyl ester (140 mg, 0.59 mmol) in 5 ml of anhydrous dimethylformamide was treated with diisopropylethylamine (154μl, 0.89mmol), hydroxy-benzotriazole (160 mg, 1.18 mmol), and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (136 mg, 0.71 mmol). After stirring for 36 h, the reaction was poured onto saturated aqueous sodium chloride and extracted with ethyl acetate (3 x 50ml) The combined organic extracts were washed twice with saturated aqueous sodium bicarbonate (2x) and saturated aqueous sodium chloride (1x), dried (Na_2SO_4), filtered, and concentrated in vacuo to give a brown oil. Chromatography (flash, SiO_2, 30% ethyl acetate/hexane) to give 160mg (61%) of 23 as a white solid: ^{1}H NMR (CDCl$_3$) δ 7.38-7.14 (10H, m), 6.85-6.8 (1H, m), 4.84-4.76 (1H, d), 4.5-4.42 (1H, m), 4.07-4.0 (1H, d), 3.78-3.72 (1H, m), 3.12-2.94 (2H, 2 x m), 2.75-2.55 (4H, m), 2.1-1.95 (2H,m), 1.5-1.45 (9H, 3 x s).

(3S)-(2-Phenethyl-[5-(3-phenylpropyl)-1H-imidazole-2-carbonyl]amino}acetyl amino) 4-oxobutanoic acid tert-butyl ester semicarbazone (24). The ester 23 (160mg, 0.357mmol) was treated with 25% trifluoroacetic acid/dichloromethane (7ml) for 4 h. The reaction was concentrated in vacuo to afford 180mg of the acid. The acid (180 mg, 0.357mmol) was coupled to (3S)-3-amino-4-oxobutanoic acid tert-butyl ester semicarbazone (161mg, 0.357mmol) as describe for the preparation of 5a and 5b to give 86 mg (33%) of 24 (one diastereomer) as a white solid : ^{1}H NMR (CDCl$_3$) δ 10.9-10.3 (1H, 2 d), 10.08-9.78 (1H, 2 d), 9.25-9.15 (1H,m), 8.35-8.10 (1H, 2 m),

7.9-7.85 (1H, 2 s), 7.40-7.05 (10H, m), 6.9-6.75
(1H,m), 6.3-5.8 (1H, br s), 5.2-4.65 (2H,m), 4.35-3.5
(3H,m), 3.25-3.0 (2H, m), 2.9-2.45 (6H,m), 2.05-1.8
(2H,m), 1.4 (9H,s).

(3S)-(2-{Phenethyl-[5-(3-phenylpropyl)-1H-imidazole-2-carbonyl]amino}acetylamino)-4-oxobutanoic acid trifluoroacetic acid salt (25) was prepared by the method described for **7a** to afford 32 mg (82%) as a white solid: ^{1}H NMR (CD$_3$OD) δ 7.05-7.35 (m, 11H), 4.65 (m, 1H), 4.4 (m, 1H), 4.3 (s, 2H), 3.6-4.0 (m, 2H), 2.5-2.95 (m, 8H), 2.05 (m, 2H).

7-[5-(3-Phenylpropyl)-1H-imidazole-2-carbonyl]-1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carboxylic acid methyl ester (26). 4-(3-Phenylpropyl)imidazole-2-carboxylic acid (**13d**) was coupled to 1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carboxylic acid methyl ester hydrobromide (Smith et. al., _J. Med. Chem._, 31, pp. 875-85 (1988)) by the method described for **23** to afford 140 mg (65%) as a yellow gum: ^{1}H NMR (CDCl$_3$) δ 7.34-7.15 (5H, m), 6.98-6.8 (1H, 3 s), 5.7-5.65 (0.5 H, m), 5.2-5.1 (1H,m), 4.82-4.75 (0.5H, m), 4.4-4.35 (1H, m), 4.05 (1H,d), 3.75-3.7 (3H, 2 s), 3.4-3.3 (4H,m), 2.95-2.45 (8H, m), 2.05-1.95 (2H,m).

(3S)-({7-[5-(3-Phenylpropyl)-1H-imidazole-2-carbonyl]-1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carbonyl}-amino)-4-oxobutanoic acid tert-butyl ester semicarbazone (27). Following the procedure described for **4**, the ester **26** was converted to its acid which was subsequently coupled to (3S)-3-amino-4-oxobutanoic acid tert-butyl ester semicarbazone as described for **24** to give 70 mg (33%) as a brown solid : ^{1}H NMR (CD$_3$OD) δ 7.28-7.10 (5H,m), 6.90 (1H, br s), 4.94 (1H, m), 3.96-3.86

(2H,q), 3.35-3.25 (4H,d), 3.0 (2H, s), 2.73-2.59 (6H, m), 2.0-1.92 (2H, m),1.44 (9H,s).

(3S)-({7-[5-(3-Phenylpropyl)-1H-imidazole-2-carbonyl]-1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carbonyl}-amino)-4-oxobutanoic acid (28) was prepared by the method described for **7a** to afford 17 mg (26%) as a light brown solid: ^{1}H NMR (CD$_3$OD) δ 7.4 (s, 1H), 7.1-7.25 (m, 5H), 4.9 (m, 1H), 4.6 (m, 1H), 4.3 (m, 1H), 3.95 (s, 2H), 3.25-3.4 (m, 4H), 3.0 (d, 2H), 2.6-2.8 (m, 5H), 2.45 (m, 1H), 2.05 (m, 2H).

29 **30** **31**

32 **33**
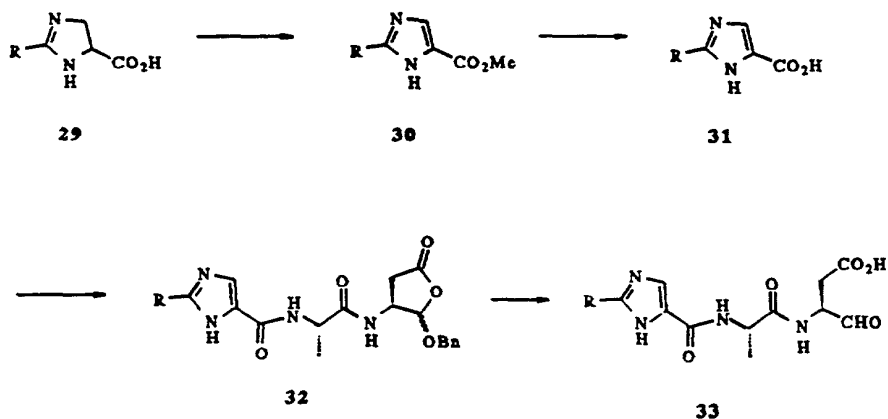
a   R = Ph(CH$_2$)$_2$
b   R = 4CF$_3$-Ph(CH$_2$)$_2$
c   R = PhCH$_2$

4,5-Dihydroimidazole-4-carboxylic esters (29) were prepared by a modification of the procedure described by Jones et al., _Tetrahedron Lett._, 29, pp. 3853-56 (1988).

(4R,S) Methyl 2-(2-phenylethyl)-4,5-dihydroimidazole-4-carboxylate (29a). Dry hydrogen chloride was bubbled

into a solution of hydrocinnamonitrile (3.28ml, 25mmol) in methanol (125ml) at 0°C for 45 mins. The solvents were removed to give the imidate salt which was dissolved in methanol (125ml) along with methyl 2,3-diaminopropionate (25mmol) (Jones et al., supra). The mixture was kept at room temperature for 2.5h, then concentrated to a yellow oil. The crude product was purified by column chromatography (10-20% methanol/dichloromethane) to afford 3.52g (61%) of a colorless glass: ^{1}H NMR(CDCl$_3$) δ 7.30-7.15 (5H, m), 4.63 (1H, t, J=9.7), 3.96 (2H, d, J=9.7), 3.72 (3H, s), 3.10 (4H, m), ^{13}C NMR(CDCl$_3$) δ 171.3, 168.8, 138.3, 128.4, 128.2, 126.6, 57.3, 53.0, 47.7, 31.7, 27.9.

(4R,S) Methyl 2-[2-(4-trifluoromethylphenyl)ethyl]-4,5-dihydroimidazole-4-carboxylate (29b), was prepared by the method described for **29a** to yield 6.80g (78%) of a colorless solid: mp. 136-141°C; ^{1}H NMR(CDCl$_3$) δ 7.45 (4H, s), 4.71 (1H, dd, J=8.6,10.8), 4.02 (2H, m), 3.73 (3H, s), 3.19 (4H, m).

Imidazole-4-carboxylic esters **30** were prepared by a modification of the procedure described by Martin et al., J. Org. Chem., 33, pp. 3758-61 (1968).

Methyl 2-(2-phenylethyl)imidazole-4-carboxylate (30a). A mixture of (4R,S) methyl 2-(2-phenylethyl)-4,5-dihydroimidazole-4-carboxylate (29a) (3.40g, 14.64mmol), chloroform (75ml) and manganese (IV) oxide (13.0g, 150mmol) was heated under reflux for 21h then filtered hot. The solids were washed with chloroform and methanol. The combined filtrates were concentrated to leave a yellow-brown solid, which was purified by column chromatography (2-5% methanol/dichloromethane) to afford 1.46g (43%) of a pale yellow solid: mp. 151-

155°C; IR (KBr) 3028, 2946, 1720, 1533, 1433, 1348, 1195, 1166; ^{1}H NMR(CDCl$_3$) δ 7.62 (1H, s), 7.26-7.02 (5H, m), 3.82 (3H, s), 3.03 (4H, brs), ^{13}C NMR(CDCl$_3$) δ 162.9, 150.2, 140.3, 128.5, 128.2, 126.3, 51.5, 34.5, 30.4. Anal. Calcd for C$_{13}$H$_{14}$N$_2$O$_2$: C, 67.81; H, 6.13; N, 12.16. Found: C, 67.70; H, 6.15; N, 12.16.

Methyl 2-[2-(4-trifluoromethylphenyl)ethyl]imidazole-4-carboxylate (30b), was prepared by the method described for **30a**. It was recrystallised from ethyl acetate to afford 1.88g (33%) of cream crystals: mp. 225-26°C; IR (KBr) 3239, 2951, 1715, 1532, 1331, 1158, 1105, 1068; ^{1}H NMR (CDCl$_3$) δ 7.61 (1H, s), 7.54 (2H, d, J = 8.1), 7.26 (2H, d, J = 8.1), 3.89 (3H, s), 3.10 (4H, m). Anal. Calcd for C$_{14}$H$_{13}$F$_3$N$_2$O$_2$: C, 56.38; H, 4.39; N, 9.39; F, 19.11. Found: C, 56.23; H, 4.44; N, 9.33; F, 19.08.

2-(2-Phenylethyl)imidazole-4-carboxylic acid (31a). A mixture of methyl 2-(2-phenylethyl)imidazole-4-carboxylate (31a) (1.38g, 6mmol), methanol (30ml) and 1M aqueous sodium hydroxide (30ml) was heated under reflux for 16h. The methanol was removed under reduced pressure, and the resulting aqueous solution was neutralized with 4M hydrochloric acid, whereupon a pale yellow solid precipitated. The precipitate was collected, washed with water, and dried to afford 1.18g (91%) of a pale yellow solid: mp. 117-120°C; IR (KBr) 3375, 3131, 2616, 2472, 1638, 1592, 1551, 1421, 1388, 1360; ^{1}H NMR(d$_6$-DMSO) δ 7.59 (1H, s), 7.26 (5H, m), 2.99 (4H, m). Anal. Calcd for C$_{12}$H$_{12}$N$_2$O$_2$ 0.25H$_2$O: C, 65.29; H, 5.71; N, 12.69. Found: C, 65.00; H, 5.64; N, 12.58.

2-[2-(4-Trifluoromethylphenyl)ethyl]imidazole-4-carboxylic acid (31b), was prepared by the method described for **31a** to afford 1.09g (76%) of a pale

yellow solid: mp. 126-130°C; IR (KBr) 3339, 2640-2467,
1638, 1589, 1545, 1383, 1323; ^{1}H NMR(d_6-DMSO) δ 7.69
(2H, d, J=8.0), 7.59 (1H, s), 7.47 (2H, d, J=8.0), 3.06
(4H, m).

5   **(2R,S, 3S) N^2-[2-(2-Phenylethyl)imidazole-4-carbonyl]-N-
(tetrahydro-2-benzyl-oxy-5-oxo-3-furanyl)-L-alaninamide
(32a).** To a solution of (2R,S, 3S) N^2-tert-
butoxycarbonyl-N-(tetrahydro-2-benzyloxy-5-oxo-3-
furanyl)-L-alaninamide (**14**) (1.59g, 4.20mmol; Chapman,
10   Biorg. Med. Chem. Lett., 2, pp. 613-18 (1992)) in
dichloromethane (15ml), cooled to 0°C, was added
trifluoroacetic acid (15ml). The mixture was stirred
at 0°C for 1h and then concentrated. The residue was
treated with ether and then the ether was removed under
15   vacuum. This procedure was repeated twice to yield a
pale yellow glass. The solid was dissolved in DMF
(20ml), then diisopropylethylamine (2.19ml, 12.6mmol),
2-(2-phenylethyl)imidazole-4-carboxylic acid (**31a**)
(1.0g, 4.62mmol), 1-(3-dimethylaminopropyl)-3-ethyl
20   carbodiimide hydrochloride (0.89g, 4.62mmol) and
hydroxybenzotriazole (1.14g, 8.40mmol) were added to
the solution. The reaction mixture was stirred at room
temperature for 20h then poured into brine. The
mixture was extracted with ethyl acetate (3 x 50ml).
25   The combined organic extracts were washed with
saturated aqueous sodium bicarbonate (3 x 100ml) then
brine (3 x 100ml), dried (MgSO$_4$) and concentrated. The
residue was purified by column chromatography (2-10%
isopropanol in dichloromethane then 0-6% isopropanol in
30   ethyl acetate) to yield 1.10g (55%) of **32a** as a mixture
of diastereomers: IR (KBr) 3278, 3065, 1790, 1641,
1577, 1545, 1499, 1454, 1120; ^{1}H NMR(CDCl$_3$) δ 10.26 (1H,
s), 8.14 (1H, s), 7.66 (d, J=7.0), 7.56 (d, J=7.0),
7.43 (1H, s), 7.31-7.11 (10H, m), 5.49 (d, J=5.6), 5.48

(s), 4.83-4.41 (4H, m), 3.04-2.41 (2H, m), 2.99 (4H,
s), 1.45 (d, J=7.0), 1.44 (d, J=7.0).

**(2R,S, 3S) N^2-{2-[2-(4-Trifluoromethylphenyl)ethyl]
imidazole-4-carbonyl}-N-(tetrahydro-2-benzyloxy-5-oxo-
3-furanyl)-L-alaninamide (32b)**, was prepared by the
method described for **32a** to afford 1.08g (62%) of a
pale yellow glass: IR (KBr) 3376, 3284, 3070, 2938,
1791, 1642, 1578, 1546, 1327, 1165, 1122, 1068;
^{1}H NMR(CDCl$_3$) δ 7.95 (0.5H, m), 7.55-7.25 (11.5H, m),
5.53 (s), 5.49 (d, J=5.3), 4.88-4.48 (4H, m), 3.11-2.96
(4H, m), 2.91 (1H, m), 2.51 (1H, m), 1.47 (3H, d,
J=7.1).

**(2R,S, 3S) N^2-(2-Benzylimidazole-4-carbonyl)-N-
(tetrahydro-2-benzyloxy-5-oxo-3-furanyl)-L-alaninamide
(32c)**, was prepared by the method described for **32a**
from 2-benzylimidazole-4-carboxylic acid (Ger. Offen.
DE 3427136) to afford 1.13g (83%) of a yellow glass:
IR (CH$_2$Cl$_2$) 3433, 3062, 2990, 1803, 1693, 1584, 1504,
1429, 1285, 1258; ^{1}H NMR(CDCl$_3$) δ 9.50 (s), 9.37 (s),
7.86 (0.5H, d, J=6.1), 7.56-7.21 (10.5H, m), 7.48 (1H,
s), 5.51 (d, J=5.2), 5.48 (s), 4.87-4.41 (4H, m), 4.08
(s), 4.07 (s), 3.03-2.39 (2H, m), 1.46 (3H, d, J=7.0).

**(3S) 3-{N-[2-(2-Phenylethyl)imidazole-4-carbonyl]-L-
alaninyl}amino-4-oxobutanoic acid (33a; A)**. A mixture
of (2R,S, 3S) N^2-[2-(2-phenylethyl)imidazole-4-
carbonyl]-N-(tetrahydro-2-benzyloxy-5-oxo-3-furanyl)-L-
alaninamide (32a) (1.0g, 2.10mmol) and 10% palladium on
activated carbon (1.0g) in methanol (50ml) was stirred
under a hydrogen atmosphere for 4.5h. The resulting
mixture was filtered and concentrated to yield a
colorless glass. Recrystallization from methanol-
diethyl ether afforded 510mg (63%) of a colorless

solid: mp. 127°C; IR (KBr) 3360, 3279, 2981, 1781, 1732, 1646, 1577, 1547; ^{1}H NMR (CD$_3$OD) δ 7.54 (1H, s), 7.29-7.12 (5H, m), 4.60-4.47 (2H, m), 4.28 (1H, m), 3.01 (4H, s), 2.76-2.39 (2H, m), 1.43 (3H, 2 x d, J=7.0, J=7.0), ^{13}C NMR (CD$_3$OD) δ 176.2, 176.0, 174.7, 174.6, 164.4, 164.3, 150.5, 141.9, 134.8, 129.5, 129.3, 127.3, 122.3, 98.8, 98.4, 52.3, 52.0, 50.3, 35.6, 31.2, 18.8, 18.7. Anal. Calcd for C$_{19}$H$_{22}$N$_4$O$_5$ H$_2$O: C, 56.43; H, 5.98; N, 13.85. Found: C, 56.78; H, 5.70; N, 13.77.

(3S) 3-{N-[2-(2-[4-Trifluoromethylphenyl]ethyl) imidazole-4-carbonyl]-L-alaninyl}-amino-4-oxobutanoic acid (33b; $\underline{C}$), was prepared by the method described for **33a** to afford 612mg (73%) of a colorless solid: mp. 120-124°C; [α]$_D^{23}$ +14.3° (c 0.5, MeOH); IR (KBr) 3287, 2985, 2937, 1782, 1732, 1646, 1579, 1547, 1327; ^{1}H NMR (CD$_3$OD) δ 7.56 (2H, d, J=8.0), 7.54 (1H, s), 7.36 (2H, d, J=8.0), 4.60-4.48 (2H, m), 4.28 (1H, m), 3.08 (4H, m), 2.75-2.41 (2H, m), 1.43 (3H, d, J=7.0). Anal. Calcd for C$_{20}$H$_{21}$F$_3$N$_4$O$_5$. 0.5H$_2$O : C, 51.84; H, 4.78; N, 12.09; F, 12.30. Found: C, 51.83; H, 4.72; N, 12.14; F, 12.36.

(3S) 3-[N-(2-Benzylimidazole-4-carbonyl)-L-alaninyl]amino-4-oxobutanoic acid (33c; $\underline{B}$), was prepared by the method described for **33a** to afford 426mg (64%) of a colorless solid: [α]$_D^{23}$ +13.4° (c 0.407, MeOH). IR (KBr) 3260, 3150, 2980, 1779, 1727, 1649, 1573, 1547; ^{1}H NMR (CD$_3$OD) δ 7.58 (1H, s), 7.34-7.22 (5H, m), 4.59-4.47 (2H, m), 4.28 (1H, m), 4.07 (2H, s), 2.74-2.41 (2H, m), 1.42 (3H, d, J=6.7); ^{13}C NMR (CD$_3$OD) δ 175.6, 175.5, 175.0, 164.6, 164.5, 150.1, 138.7, 135.3, 130.0, 129.9, 128.2, 122.9, 98.9, 98.5, 52.5, 52.2, 35.5, 35.1, 35.0, 19.0, 18.9. Anal. Calcd for C$_{18}$H$_{20}$N$_4$O$_5$ H$_2$O: C, 55.37; H, 5.68; N, 14.35. Found C,

55.83; H, 5.75; N, 13.96. MS(FAB, m/z) : 373 ((M⁺),
228, 185, 91.

(a) R = H
(b) R = CH₂Ph
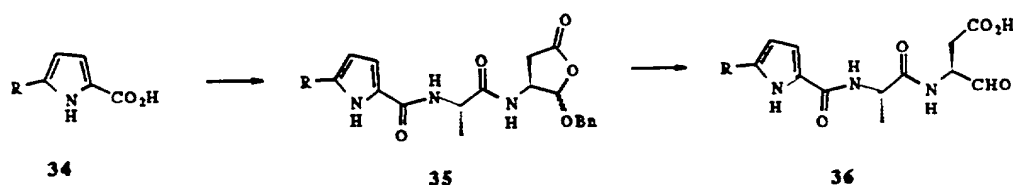
5-Benzylpyrrole-2-carboxylic acid (34b). A mixture of
5   Ethyl 5-benzylpyrrole-2-carboxylate (0.7g, 3.05mmol;
Elder et al., _Synthetic Communications_, 19, 763-767
(1989)), ethanol (20ml) and 1M sodium hydroxide (9.2ml,
9.2mmol) was stirred and heated under reflux for 3h.
10 The major part of the ethanol was removed and the
remaining liquid was diluted with water, washed with
ether, cooled in ice and acidified with concentrated
hydrochloric acid. The mixture was extracted with
ether. The combined extracts were washed with brine,
15 dried (Na₂SO₄) and concentrated to afford 0.567g (92%)
of an off white solid: mp. 130-134°C; ¹H NMR(CDCl₃) δ
8.87 (1H, brs), 7.37-6.95 (5H, m), 6.97 (1H, m), 6.07
(1H, m), 4.00 (2H, s).

(2R,S, 3S) N²-(Pyrrole-2-carbonyl)-N-(tetrahydro-2-
20 **benzyloxy-5-oxo-3-furanyl)-L-alaninamide (35a).** A
solution of (2R,S, 3S) N²-tert-butoxycarbonyl-N-
(tetrahydro-2-benzyloxy-5-oxo-3-furanyl)-L-alaninamide
(14) (756mg, 2.0mmol) in dry dichloromethane (8ml) at
0°C was treated with trifluoroacetic acid (8ml) for 1h
25 and then evaporated to dryness. Dry ether was added to
the residue and the mixture concentrated to give a
viscous oil. The oil was dissolved in dry DMF (10ml).

Pyrrole-2-carboxylic acid (**34a**) (244mg, 2.2mmol) was added and the solution was cooled in an ice bath before the addition of N,N-diisopropylamine (0.78g, 6.0mmol), 1-hydroxybenzotriazole (0.54g, 4.0mmol) and ethyl dimethylaminopropyl carbodiimide hydrochloride (0.42g, 2.2mmol). The resulting mixture was stirred at 25°C for 17h and then saturated aqueous sodium chloride (30ml) was added. The mixture was extracted with ethyl acetate (3 x 20ml) and the combined organic extracts were washed with 5% aqueous sodium bicarbonate (3 x 10ml) and brine (10ml), dried ($MgSO_4$) and concentrated. Flash chromatography (25% hexane-ethyl acetate) afforded 557mg (75%) of a 1:1 mixture of diastereomers as a white glassy solid: mp. 85-90°C; IR (KBr) 3288, 1789, 1665, 1629, 1557 and 1122; ^{1}H NMR(d_6-DMSO) δ 11.46 (1H, bs), 8.55 (0.5H, d, J=7.0), 8.30 (0.5H, d, J=7.6), 8.06 (0.5H, d, J=7.0), 8.04 (0.5H, d, J=7.6), 7.36-7.30 (5H, m), 6.88-6.85 (2H, m), 6.10-6.07 (1H, m), 5.63 (0.5H, d, J=5.0), 5.42 (0.5H, s), 4.72 (2H, q, J=12.2), 4.74-4.25 (2H, m), 3.14-2.35 (2H, m), 1.29, 1.25 (3H, 2 x d, J=7.2).

(2*R*,*S*, 3*S*) N^2-(5-Benzylpyrrole-2-carbonyl)-N-(tetrahydro-2-benzyloxy-5-oxo-3-furanyl)-L-alaninamide (35b), was prepared from 5-benzylpyrrole-2-carboxylic acid (**34b**) by the method described for compound **35a** (65%). Data is given for a single diastereomer. ^{1}H NMR (d_6-DMSO) δ 11.37 (1H, brs,), 8.27 (1H, d, J=7.4), 7.93 (1H, d, J=7.6), 7.33-7.16 (10H, m), 6.76 (1H, m), 5.82 (1H, m), 5.62 (1H, d, J=5.2), 4.76 (1H, d, J=12.0), 4.65 (1H, m), 4.62 (1H, d, J=12.2), 4.47 (1H, m), 3.88 (2H, s), 2.77 (1H, dd, J=9.0,18.0), 2.5 (dd), 1.23 (3H, d, J=7.0).

(3*S*) 3-[N-(Pyrrole-2-carbonyl)-L-alaninyl]amino-4-
oxobutanoic acid (36a; **D**). A mixture of (35a) (612mg;
1.65mmol), methanol (40ml) and 10% palladium on carbon
(500mg) was vigorously stirred under an atmosphere of
hydrogen for 4h. The mixture was filtered through a
0.2μM nylon membrane then concentrated. The residue
was purified by flash chromatography (5-10% methanol in
methylene chloride) to afford the hemihydrate of (36a)
(223mg, 48%) as a white solid after precipitation from
an ethyl acetate-ether mixture. There were traces of
solvent in the product: mp. 96-100°C; IR (KBr) 3381,
1774, 1729 (EtOAc), 1632, 1558, 1523, 1123;
^{1}H NMR(CD$_3$OD) δ 6.94-6.85 (2H, m), 6.17 (1H, dd, *J*=3.8
and 2.6), 4.58 (0.5H, d, *J*=3.94), 4.56 (0.5H, d,
J=4.24), 4.51 (1H, q, *J*=7.16), 4.35-4.20 (1H, m), 2.74-
2.40 (2H, m), 1.42 and 1.41 (3H, 2 x d, *J*=7.13).

(3*S*) 3-[N-(5-Benzylpyrrole-2-carbonyl)-L-
alaninyl]amino-4-oxobutanoic acid (36b), was prepared
(41%) from 35b by the method described for compound
36a, to afford an off white solid: mp. 109-112°C; [α]$_D^{25}$
+6.3° (c 0.3, methanol); IR (KBr) 3368, 1724, 1630,
1530, 1453, 1414, 1233, 1049; ^{1}H NMR(d$_4$ methanol) δ
7.25-7.11 (5H, m), 6.76 (1H, d, *J*=3.5), 5.84 (1H, d,
J=3.5), 4.51 (1H, m), 4.43 (1H, q, *J*=7.1), 4.23 (1H,
m), 2.5 (2H, m),1.35 (3H, d, *J*=7.0). Anal. Calcd for
C$_{19}$H$_{21}$N$_3$O$_5$. 1.75 H$_2$O: C, 56.64; H, 6.13; N, 10.43. Found:
C, 56.34; H, 5.72; N, 10.00.

38   **39**
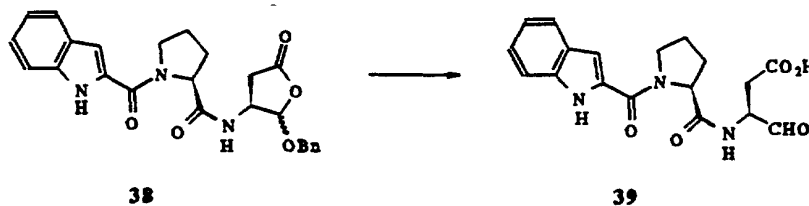
(2R,S, 3S) 1-(Indole-2-carbonyl)-N-(tetrahydro-2-benzyloxy-5-oxo-3-furanyl)-L-prolinamide (38).
Trifluoroacetic acid (4ml) was added to a solution of
(2R,S, 3S) 1-tert-butoxycarbonyl-N-(tetrahydro-2-
5   benzyloxy-5-oxo-3-furanyl)-L-prolinamide (15) (0.607g,
1.5mmol) in dichloromethane (4ml) at 0°C. The mixture
was stirred at 0°C for 75 min. The mixture was
concentrated, and the residue treated with diethyl
ether, then the ether was removed under vacuum. This
10   procedure was repeated twice to yield a yellow oil,
which was dissolved in DMF (12ml). Diisopropyl-
ethylamine (0.78ml, 4.5mmol) followed by indole-2-
carboxylic acid (266mg, 1.65mmol), 1-(3-
dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride
15   (316mg, 1.65mmol) and hydroxybenzotriazole (405mg,
3mmol) were then added to the solution. The mixture
was stirred at room temperature for 20h then poured
into brine. The mixture was extracted with ethyl
acetate (3 x 30ml). The combined organic extracts were
20   washed with saturated aqueous sodium bicarbonate (2 x
60ml) then brine (2 x 60ml), dried (MgSO$_4$), filtered and
concentrated. The residue was purified by column
chromatography (ethyl acetate) to afford 518mg (77%) of
a mixture of diastereomers: IR (KBr) 3314, 1780, 1677,
25   1609, 1524, 1435, 1406, 1344; ^{1}H NMR (d$_6$-DMSO), δ 11.58
(1H, m), 8.81-8.41 (1H, m), 7.71-6.67 (10H, m), 5.70
(d, J=5.2), 5.48 (s), 4.89-4.29 (4H, m), 3.99-3.74 (2H,
m), 3.20-2.44 (2H, m), 2.39-1.77 (4H, m).

(3S) 3-[1-(Indole-2-carbonyl)-L-prolinyl]amino-4-
30   **oxobutanoic acid (39).** A mixture of (2R,S, 3S) 1-
(indole-2-carbonyl)-N-(tetrahydro-2-benzyloxy-5-oxo-3-
furanyl)-L-prolinamide (38) (478mg, 1.07mmol) and 10%
palladium on carbon (475mg) and methanol (150ml) was
stirred under a hydrogen atmosphere for 6h. The

resulting mixture was filtered and concentrated to
yield a colorless glass. Recrystallization from a
mixture of methanol and diethyl ether afforded 202mg
(53%) of a colorless solid: mp. 135-138°C; $[\alpha]_D^{24}$ -44° (c

5   0.25, CH_3OH);   IR (KBr) 3287, 2977, 2879, 1781, 1725,
1716, 1667, 1662, 1600, 1529, 1441, 1346; ^1H NMR(CD_3OD)
δ 7.65 (1H, d, J=8.0), 7.44 (1H, d, J=8.4), 7.22 (1H,
m), 7.09-6.84 (2H, m), 4.62 (2H, m), 4.29 (1H, m),
4.15-3.73 (2H, m), 2.74-1.72 (6H, m).

10

40

41

42

43
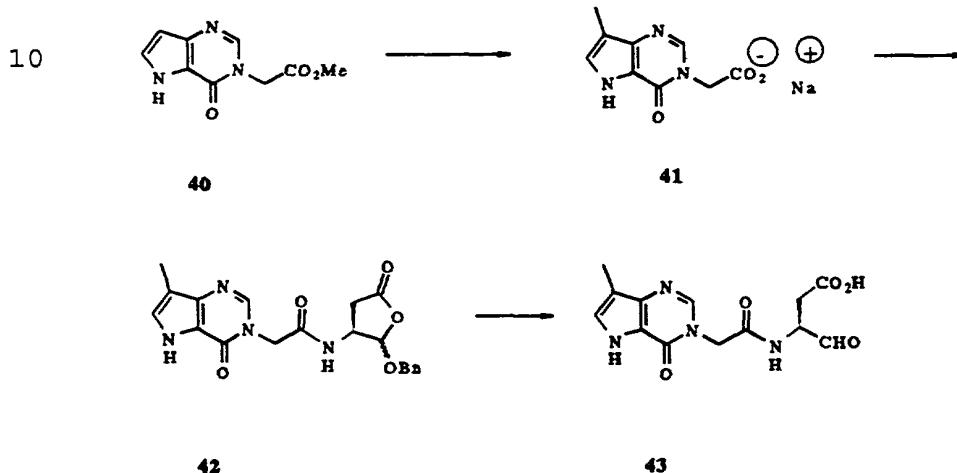
**Methyl 2-(3,5-dihydro-7-methyl-4-oxo-4H-pyrrolo
[3,2-d] pyrimidin-3-yl)acetate (40).** Freshly prepared
methyl glycinate (1.25g, 14mmol) was added to a stirred

15   solution of ethyl 3-[N-(dimethylamino) methylene]amino-
4-methylpyrrole-2-carboxylate (1.56g, 7.0mmol; Lim et
al., _J. Org. Chem._, 44, pp. 3826-29 (1979)) in dry
methanol (60ml). The resulting mixture was kept at
70°C. Two further batches of methyl glycinate (1.25,

20   14.0mmol) were added after 18h and 42h heating. The
mixture was cooled and filtered 24h after the final
addition. The filtrate was concentrated and the
residue purified by flash chromatography (2-5%

methanol/chloroform) to afford 0.54g (35%) of a white crystalline solid: mp. 233-235°C (recrystallized from ethyl acetate); IR (KBr) 3135, 2958, 1745, 1675, 1254; ^{1}H NMR (d$_6$-DMSO) δ 11.90 (1H, s), 8.07 (1H, s), 7.23 (1H, s), 4.83 (2H, s), 3.69 (3H, s), 2.16 (3H, s). Anal. Calcd for C$_{10}$H$_{11}$N$_3$O$_3$ 0.1H$_2$O: C, 53.85; H, 5.07; N, 18.84. Found: C, 53.85; H, 4.96; N, 18.81; MS(70eVE.I.) m/e 222, 221 (M$^+$, 100%), 189, 162, 133, 105.

2-(3,5-Dihydro-7-methyl-4-oxo-4H-pyrrolo[3,2-d]pyrimidin-3-yl)acetic acid, sodium salt (41). A suspension of **40** (354mg, 1.6mmol) in methanol (15ml) was treated with 0.5N sodium hydroxide (4.8ml) and the resulting mixture was stirred at 25°C for 1h. The reaction mixture was filtered to afford the hemihydrate of **41** (354mg, 97%) as a white crystalline solid : mp. >340°C (recrystallized from methanol); IR (KBr) 3461, 3143, 1676, 1666, 1605, 1415; ^{1}H NMR(d$_6$ DMSO) δ 11.63 (1H, s), 7.83 (1H, s), 7.11 (1H, d, J=2.0), 4.24 (2H, s), 2.14 (3H, s). Anal. Calcd for C$_9$H$_8$N$_3$O$_3$Na. 0.5H$_2$O: C, 45.39; H, 3.81; N, 17.64. Found: C, 45.57; H, 4.05; N, 17.39.

(2R,S, 3S) 2-(3,5-Dihydro-7-methyl-4-oxo-4H-pyrrolo[3,2-d]pyrimidin-3-yl)-N-(tetrahydro-2-benzyloxy-5-oxo-3-furanyl)acetamide (42). A suspension of the sodium salt **41** (344mg, 1.5mmol) in dry DMF (15ml) was treated with ethyl dimethylaminopropyl carbodiimide hydrochloride (373mg, 1.95mmol) and 1-hydroxybenzo-triazole (405mg, 3.0mmol). The mixture was kept at 25°C for 1h then (2R,S, 3S) N-allyloxycarbonyl-3-amino-2-benzyloxy-5-oxotetrahydrofuran (437mg, 1.5mmol; Chapman, Biorg. Med. Chem. Lett., 2, pp. 613-18 (1992)) and (Ph$_3$P)$_2$PdCl$_2$

(25mg) were added followed by the dropwise addition of n-tributyltin hydride (0.6ml, 2.25mmol). The resulting mixture was stirred at 25°C for 1h then water (20ml) was added. The mixture was extracted with ethyl acetate (3 x 15ml), and the combined organic extracts were washed with water (5ml), dried (MgSO$_4$), and concentrated to afford a mixture of diastereomers. Evaporation of the aqueous phase and purification of the residue by flash chromatography (5% methanol/chloroform) gave an additional quantity affording a total 182mg of **42** (31%) : m.p. 240-244°C; IR (KBr) 3274, 1772, 1691, 1664, 1562; ^{1}H NMR (d$_6$-DMSO) δ 11.81 (1H, s), 8.85 (0.6H, d, J=6.6), 8.72 (0.4H, d, J=7.4), 7.98 (0.6H, s), 7.95 (0.4H, s), 7.40-7.30 (5H, m), 7.20 (1H, d, J=2.2), 5.61 (0.4H, d, J=5.0), 5.46 (s), 4.85-4.60 (m), 4.28 (m), 3.20-2.35 (2H, m), 2.16 (3H, s).

(3S)-3-[2-(3,5-Dihydro-7-methyl-4-oxo-4H-pyrrolo[3,2-d]pyrimidin-3-yl)-1-oxo-ethylamino]-4-oxobutanoic acid (43). A mixture of **42** (131mg, 0.33mmol), in methanol (50ml) and 10% palladium on carbon (100mg) was stirred vigorously under an atmosphere of hydrogen for 2h. An additional quantity of catalyst (100mg) was added and the mixture hydrogenated for a further 2h. The mixture was filtered through a 0.2μM nylon membrane, and concentrated. The residue was recrystallized from methanol/diethyl ether to afford 79mg (78%) of **43** as a hygroscopic white solid: mp. 222-226°C; (decomp.); [α]$_D^{32}$ +0.5 (c 0.02, MeOH); IR (KBr) 3282, 1680, 1558, 1425 1275; ^{1}H NMR (CD$_3$OD) δ 8.03 (1H, s), 7.18 (1H, d, J=0.7), 4.79-4.74 (2H, m), 4.63-4.59 (1H, 2 x d, J=3.6), 4.36-4.25 (1H, m), 2.78-2.39 (2H, m), 2.24 (3H, d, J=0.7). Anal. Calcd for C$_{13}$H$_{14}$N$_4$O$_5$. 1.4H$_2$O: C, 47.10; H, 5.12; N, 16.90. Found: C, 47.00; H, 4.79; N, 16.59.

FABMS m/e 307, 306 (M⁺), 244, 207, 190, 152, 115 (100%).

FABMS m/e 307, 306 (M^+), 244, 207, 190, 152, 115 (100%).
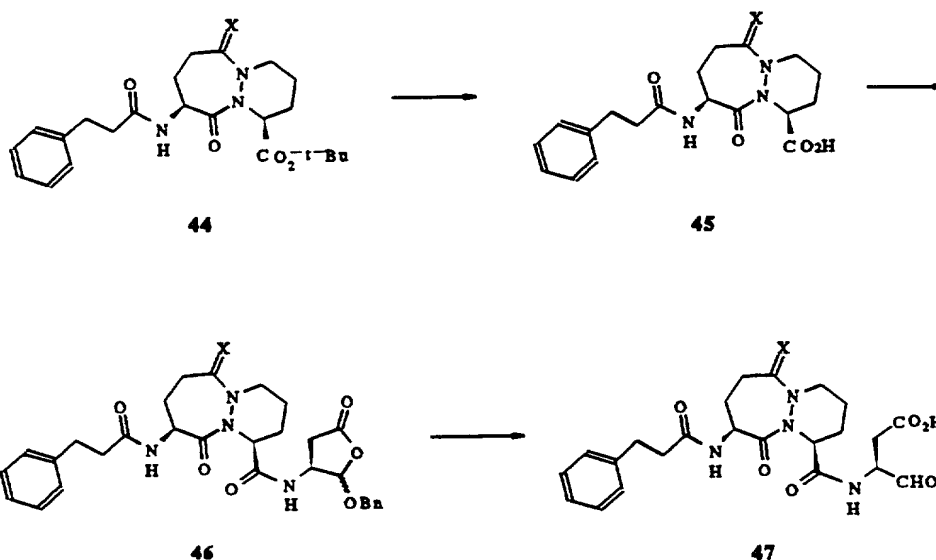
(a) X = O
(b) X = H$_2$

5   (1S,9S) t-Butyl 6,10-dioxo-octahydro-9-(3-
     phenylpropionylamino)-6H-pyridazino[1,2-a]
     [1,2]diazepine-1-carboxylate (44a). To a solution of
     (1S,9S)t-butyl 9-amino-6,10-dioxo-octahydro-6H-
     pyridazino [1,2-a][1,2]diazepine-1-carboxylate (690mg;
10   2.32mmol; GB 2128984) in dioxane (16ml) and water (4ml)
     at 0°C was added solid sodium bicarbonate (292mg;
     3.48mmol) followed by dropwise addition of 3-
     phenylpropionyl chloride (470mg; 2.78mmol). The
     mixture was stirred at room temperature for 2h then
15   more sodium bicarbonate (200mg; 2.38mmol) and 3-
     phenylpropionyl chloride (100mg; 0.6mmol) was added.
     The mixture was stirred for a further 2h at room
     temperature, diluted with ethyl acetate (50ml), washed

with saturated sodium bicarbonate (2 x 25ml) then dried
(MgSO$_4$) and concentrated. The residue was purified by
flash chromatography (0-50% ethyl acetate/chloroform)
and finally crystallized by trituration with ether to
afford 860mg (86%) of a white solid: mp. 137-138°C;
$[\alpha]_D^{23}$ -95.1° (c 0.549, CH$_2$Cl$_2$); IR (KBr) 3327, 1736,
1677, 1664, 1536, 1422, 1156; ^{1}H NMR (CDCl$_3$) δ 7.24 (5H,
m), 6.50 (1H, d, J=7.5), 5.24 (1H, m), 4.90 (1H, m),
4.60 (1H, m), 3.44 (1H, m), 2.93 (2H, m), 2.84 (1H, m),
2.64 (1H, m), 2.54 (2H, m), 2.26 (2H, m), 1.70 (4H, m),
1.70 (9H, s). MS(FAB, m/z): 430 (M$^+$ + 1), 374, 242,
105, 91.

**(1S,9S)t-Butyl octahydro-10-oxo-9-(3-
phenylpropionylamino)-6H-pyridazino-[1,2-a]
[1,2]diazepine-1-carboxylate (44b)**, was prepared from
(1S, 9S)-t-butyl 9-amino-octahydro-10-oxo-6H-
pyridazino[1,2-a][1,2]diazepine-1-carboxylate (Attwood
et al., J. Chem. Soc. Perkin 1, pp. 1011-19 (1986)) as
for **44a**, to afford 810mg (81%) of a colorless oil:
$[\alpha]_D^{23}$ - 33.5° (c 0.545, CH$_2$Cl$_2$); IR (film) 3334, 2935,
1737, 1728, 1659, 1642; ^{1}H NMR (CDCl$_3$) δ 7.24 (5H, m),
6.75 (1H, d, J=6.7), 5.27 (1H, m), 4.92 (1H, m), 3.39
(1H, m), 3.03 (4H, m), 2.55 (3H, m), 2.33 (1H, m), 2.17
(1H, m), 1.80 (5H, m), 1.47 (9H, s), 1.39 (1H, m).
MS(FAB, m/z): 416 (M$^+$ + 1), 360, 211, 143, 97.

**(1S,9S) 6,10-Dioxo-octahydro-9-(3-
phenylpropionylamino)-6H-pyridazino[1,2-a]
[1,2]diazepine-1-carboxylic acid (45a).** To a solution
of (1S,9S) t-butyl 6,10-dioxo-octahydro-9-(3-
phenylpropionylamino)-6H-pyridazino[1,2-a]
[1,2]diazepine-1-carboxylate (44a) (800mg; 1.863mmol)
in dry dichloromethane (5ml) at 0°C was added
trifluoroacetic acid (5ml). The solution was stirred

at room temperature for 3h then concentrated. Dry ether (10ml) was added to the residue then removed under vacuum. This process was repeated three times to afford a crystalline solid. The solid was triturated with ether and filtered to afford 590mg (85%) of a white crystalline solid: mp. 196-197.5°C; $[\alpha]_D^{23}$ -129.5° (c 0.2, CH_3OH); IR (KBr) 3237, 1729, 1688, 1660, 1633, 1574, 1432, 1285, 1205; ^1H NMR (CD_3OD) δ 8.28 (1H, d, J=7.4), 7.22 (5H, m), 5.32 (1H, dd, J=5.9, 2.9), 4.75 (1H, m), 4.51 (1H, m), 3.50 (1H, m), 3.01 (1H, m), 2.91 (2H, m), 2.55 (2H, m), 2.29 (3H, m), 1.95 (2H, m), 1.71 (2H, m). Anal. Calcd for $C_{19}H_{23}N_3O_5$: C, 61.12; H, 6.21; N, 11.25. Found: C, 60.80; H, 6.28; N, 10.97. MS(FAB, m/z) 374 (M^+ + 1), 242, 105, 91.

(1*S*, 9*S*) Octahydro-10-oxo-9-(3-phenylpropionylamino)-6H-pyridazino[1,2-a]-[1,2]diazepine-1-carboxylic acid (45b), was prepared from (1*S*, 9*S*) t-butyl octahydro-10-oxo-9-(3-phenylpropionylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylate (44b) by the method described for compound **45a** to afford 657mg (96%) of **45b** as a crystalline solid: mp. 198-202°C; $[\alpha]_D^{23}$ -86.2° (c 0.5, CH_3OH); IR (KBr) 3294, 2939, 1729, 1645, 1620, 1574, 1453, 1214; ^1H NMR (CD_3OD) δ 7.92 (1H, d, J=7.9), 7.20 (5H, m), 5.29 (1H, m), 4.90 (1H, m), 3.47 (1H, m), 3.08 (2H, m), 2.90 (2H, m), 2.55 (3H, m), 2.36 (1H, m), 1.81 (5H, m), 1.43 (2H, m). MS(FAB, m/z) 360 (M^+ +1), 211,143,91.

[3*S*, 2*R*,*S*, (1*S*,9*S*)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-octahydro-9-(3-phenylpropionylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (46a). To a solution of (1*S*, 9*S*) 6,10-dioxo-octahydro-9-(3-phenyl-propionylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylic acid (45a) (662mg;

1.773mmol) in dry dichloromethane (9ml) and dry
dimethyl formamide (3ml) at room temperature was added
bis(triphenylphosphine)palladium chloride (30mg) and
(3S, 2R,S)-3-allyloxycarbonylamino-2-benzyloxy-5-
oxotetrahydrofuran (Chapman, Biorg. Med. Chem. Lett.,
2, pp. 613-18 (1992)) (568mg; 1.95mmol) followed by
dropwise addition of tri-n-butyltin hydride (1.19g;
4.09mmol). 1-Hydroxy-benzotriazole (479mg; 3.546mmol)
was added to the mixture and the mixture was cooled to
0°C before addition of 1-(3-dimethylaminopropyl)-3-
ethylcarbodiimide hydrochloride (408mg; 2.128mmol).
The mixture was stirred at room temperature for 3.25h
then diluted with ethyl acetate (50ml), washed twice
with dilute hydrochloric acid (20ml), twice with
saturated sodium bicarbonate (20ml), once with brine
then dried (MgSO$_4$) and concentrated. The resulting oil
was purified by flash chromatography (0-100% ethyl
acetate/chloroform) to afford 810mg (81%) of **46a** as a
mixture of anomers: mp. 92-94°C; IR (KBr) 3311, 1791,
1659, 1651, 1536; ^{1}H NMR(CDCl$_3$) δ 7.49, 6.56 (1H, 2d,
J=6.7, 7.8), 7.29 (10H, m), 6.37, 6.18 (1H, 2d,
J=7.7,7.6), 5.56, 5.34 (1H, d, s, J=5.2), 5.08-4.47
(6H), 3.18-2.80 (5H), 2.62-2.28 (5H), 2.04-1.53 (5H).
MS(FAB, m/z), 563 (M$^+$ + 1), 328, 149, 91.

[3S, 2R,S, (1S, 9S)] **N-(2-Benzyloxy-5-**
oxotetrahydrofuran-3-yl)-octahydro-10-oxo-9-(3-
phenylpropionylamino)-6H-pyridazino[1,2-a]
[1,2]diazepine-1-carboxamide (46b), was prepared from
45b by the method described for **46a** to yield 790mg
(96%) of a glass: m.p. 58-60°C; IR (KBr) 3316, 2940,
1793, 1678, 1641, 1523, 1453, 1120; ^{1}H NMR (CDCl$_3$) δ
7.28 (10H, m), 6.52, 6.42 (1H, 2d, J=7.2, 7.1), 5.53,
5.44 (1H, d, s, J=5.2), 5.35 (1H, m), 4.6-4.9, 4.34
(4H, m), 3.1-2.8 (6H, m), 2.6-2.1 (7H), 1.95-1.05 (5H).

MS(FAB, m/z), 549 (M$^+$ + 1), 400, 310, 279, 91.

[3S, (1S, 9S)] 3-(6,10-Dioxo-octahydro-9-(3-phenylpropionylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (47a).
A mixture of [3S, 2R,S, (1S, 9S)] N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-octahydro-9-(3-phenylpropionylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (**46a**) (205mg; 0.364mmol), 10% palladium on carbon (200mg) and methanol (20ml) was stirred under hydrogen at atmospheric pressure for 5h. The mixture was filtered then concentrated to yield 154mg (90%) of a glass: mp. 116-118°C; $[\alpha]_D^{23}$ -140° (c 0.1, CH$_3$OH); IR (KBr) 3323 (br), 1783, 1731, 1658, 1539, 1455, 1425; ^{1}H NMR (CD$_3$OD) δ 7.21 (5H, m), 5.17 (1H, m), 4.73 (1H, m), 4.50 (2H, m), 4.23 (1H, m), 3.38 (1H, m), 3.06 (1H, m), 2.91 (2H, m), 2.73-2.18 (6H, m) and 2.01-1.59 (5H, m). Anal. Calcd for C$_{23}$H$_{27}$N$_4$O$_7$ + H$_2$O : C, 56.32; H, 6.16; N, 11.42. Found: C, 56.29; H, 6.11; N, 11.25. MS(FAB, m/z) 473 (M$^+$ + 1), 176, 149, 105, 91.

[3S, (1S,9S)]3-(Octahydro-10-oxo-9-(3-phenylpropionylamino)-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (47b),
was prepared from **46b** by the method described for **47a**. The residue was purified by flash chromatography (0-10% methanol/chloroform) to afford 65mg (52%) of a glass; m.p. 87-90°C; $[\alpha]_D^{23}$ -167.0° (c 0.1, methanol); IR (KBr) 3329, 2936, 1786, 1727, 1637; ^{1}H NMR (CD$_3$OD) δ 7.23 (5H, m), 5.29 (1H, m), 4.83 (1H, m), 4.59 (1H, d, J=3.6), 4.29 (1H, m), 3.3-3.0 (3H, m), 2.91 (2H, m), 2.70-2.34 (5H, m), 2.19 (2H, m), 1.75 (4H, m), 1.36 (2H, m). Anal. Calcd for C$_{23}$H$_{30}$N$_4$O$_6$ + 0.5H$_2$O: C, 59.09; H, 6.68; N, 11.98. Found: C, 58.97; 6.68; N, 11.73. MS(FAB, m/z) 459 (M$^+$ + 1), 310, 149, 105, 91.

	R_1	R_2	R_3
(a)	$PhCH_2$	H	(S)Me
(b)	$PhCH_2$	CH_2Ph	H
(c)	$PhCH_2$	$(CH_2)_2Ph$	H
(d)	$PhCH_2$	nBu	H
(e)	$PhCH_2$	Me	H
(f)	$PhCH_2$	Ph	H
(g)	$PhCH_2$	H	H
(h)	$PhCH_2$	CH_2Ph	(S)-Me
(i)	$Ph(CH_2)_2$	CH_2Ph	H

Pyridones **48** were prepared by the method described by Damewood et al., _J. Med. Chem._, 37, pp. 3303-12 (1994)). Compound **48d** is new.

3-Benzyloxycarbonylamino-6-butyl-pyrid-2-one (48d), was isolated as a cream solid: mp. 158-160°C; IR (KBr) 3382, 2953, 2930, 2866, 1729, 1643, 1524, 1468, 1202, 1044; ^1H NMR (d_6-DMSO) δ 8.26 (1H, s), 7.72 (1H, d), 7.39 (5H, m), 6.00 (1H, d), 5.14 (2H, s), 2.41 (2H, t), 1.52 (2H, m), 1.24 (2H, m), 0.87 (3H, t). Anal. Calcd for $C_{17}H_{20}N_2O_3$: C, 67.98; H, 6.71; N, 9.33. Found: C, 67.69; H, 6.68; N, 9.20. MS CI M^+ = 300 (m)) 28%.

(2S) Methyl 2-[3-benzyoxycarbonylamino-1,2-dihydro-2-oxo-1-pyridyl]propionate (49a). Sodium hydride (80% oil dispersion) (0.35g, 11.64mmole) was added to a stirred mixture of 3-(benzyloxycarbonylamino)pyrid-2-

one (**48a**) (2.58g, 10.58mmol) and tetrahydrofuran
(100ml) at room temperature. The mixture was stirred
for 10 mins. The resulting solution was added to a
solution of 2(*R*) methyl-2((trifluoromethane)

5   sulphonyloxy)propionate (2.5g, 10.58mmole; Feenstra et
al., <u>Tetrahedron Lett.</u>, 28, pp. 1215-18 (1987)) in
tetrahydrofuran (5ml) at room temperature during 10
mins. The mixture was stirred at room temperature for
80 mins then poured into ethyl acetate. The mixture

10   was washed twice with 1M HCl, twice with aqueous sodium
bicarbonate then brine. It was dried (MgSO$_4$) and
concentrated. The residue was purified by flash
chromatography (30% ethyl acetate/hexane) to afford
2.945g (84%) of a colorless solid: mp. 96-7°; $[\alpha]_D^{20}$ -

15   71.36 (c 2.5, CHCl$_2$); IR (KBr) 3370, 1764, 1729, 1648,
1602, 1564, 1523, 1515, 1503, 1449, 1359, 1203, 1064;
^{1}H NMR(CDCl$_3$) δ 8.04 (1H, d, *J*=7.2), 7.86 (1H, s), 7.36
(5H, m), 6.98 (1H, dd, *J*=7.1, *J*=1.7), 6.30 (1H, t,
J=7.2), 5.46 (1H, q, *J*=7.4), 5.20 (2H, s), 3.74 (3H,

20   s), 1.66 (3H, d, *J*=7.4). Anal. Calcd for C$_{17}$H$_{18}$N$_2$O$_5$: C,
61.81; H, 5.49; N, 8.48. Found: C, 61.49; H, 5.51; N,
8.41. MS(FAB, m/z) 331 (M$^+$ + 1), 299, 223, 196, 163,
91.

Methyl [6-benzyl-3-benzyloxycarbonylamino-1,2-dihydro-
25   **2-oxo-1-pyridyl]-acetate (49b).** Sodium hydride (80%
oil dispersion) (0.65g, 26.2mmole) was added to a
stirred mixture of 6-benzyl-3(benzyloxycarbonylamino)
pyrid-2-one (**48b**) (7.3g, 2.18mmol) and tetrahydrofuran
(150ml) at room temperature. The mixture was stirred

30   for 10mins, treated with methyl bromoacetate (2.5ml,
26.2mmol) and kept for 3h. The resulting mixture was
poured onto a mixture of ice and 1M HCl. The resulting
solid was filtered off then dissolved in
dichloromethane. The resulting solution was dried

(MgSO$_4$), decolourized with charcoal and concentrated. The residue was purified by chromatography (2-5% ethyl acetate/dichloromethane) to afford 7.2g (81%) of colorless crystals: mp. 117-9°; IR (KBr) 3375, 1753, 1730, 1651, 1605, 1513, 1384, 1223, 1185, 1071; ^{1}H NMR (CDCl$_3$) δ 8.02 (1H, d, J=7.5), 7.78 (1H, s), 7.31 (8H, m), 7.10 (2H, m), 6.15 (1H, d, J=7.5), 5.20 (2H, s), 4.70 (2H, s), 3.88 (2H, s), 3.66 (3H, s).

The following compounds were prepared in a similar manner:

Methyl [3-benzyloxycarbonylamino-1,2-dihydro-2-oxo-6-phenethyl-1-pyridyl]-acetate (49c). 97% yield: m.p. 102-4°C. IR (KBr) 3245, 3232, 1741, 1725, 1648, 1600, 1526, 1216; ^{1}H NMR (d$_6$-DMSO) δ 8.45 (1H, s), 7.76 (1H, d, J = 7.6), 7.35 (10H, m), 6.15 (1H, d, J = 7.6), 5.15 (2H, s), 4.85 (2H, s), 3.68 (3H, s), 2.86 (4H, s).

Methyl [3-benzyloxycarbonylamino-6-butyl-1,2-dihydro-2-oxo-1-pyridyl]-acetate (49d). 90% yield: mp. 111-112°C; IR (KBr) 3393, 1738, 1731, 1645, 1598, 1517, 1225, 1208; ^{1}H NMR (d$_6$-DMSO) δ 8.39 (1H, s), 7.78 (1H, d, J = 7.7), 7.35 (5H, m), 6.17 (1H, d, J = 7.7), 5.15 (2H, s), 4.80 (2H, s), 3.67 (3H, s), 1.38 (6H, m), 0.89 (3H, t).

Methyl [3-benzyloxycarbonylamino-1,2-dihydro-6-methyl-2-oxo-1-pyridyl]-acetate (49e). 84% yield as a colorless solid: mp. 115-6°C; IR (KBr) 3246, 1740, 1725, 1649, 1598, 1573, 1535, 1417, 1365, 1259, 1219, 1193, 1090, 1068, 1006; ^{1}H NMR (d$_6$-DMSO) δ 8.40 (1H, s), 7.75 (1H, d, J = 7.6), 7.38 (5H, m), 6.20 (1H, d, J = 7.6), 5.15 (2H, s), 4.85 (2H, s), 3.68 (3H, s), 2.26 (3H, s).

Methyl [3-benzyloxycarbonylamino-1,2-dihydro-6-phenyl-1-pyridyl]-acetate (49f). 67% yield as a colorless oil: IR (KBr) 3266, 1739, 1727, 1646, 1606, 1566, 1517, 1490, 1365, 1213, 1163, 1075; ^{1}H NMR (CDCl$_3$) δ 8.15 (1H, d), 7.85 (1H, s), 7.39 (10H, m), 6.22 (1H, d), 5.22 (2H, s), 4.57 (2H, s), 3.74 (3H, s).

Methyl [3-benzyloxycarbonylamino-1,2-dihydro-2-oxo-1-pyridyl]-acetate (49g). 80% yield as a colorless crystalline solid: m.p. 110-111°C. IR (KBr) 3385, 1745, 1726, 1650, 1601, 1512, 1502, 1378, 1369, 1358, 1215, 1195, 1162, 1067; ^{1}H NMR (CDCl$_3$) δ 8.06 (1H, d), 7.84 (1H, s), 7.36 (5H, m), 6.88 (1H, dd), 6.27 (1H, t), 5.20 (2H, s), 4.68 (2H, s), 3.78 (3H, s). Anal. Calcd for C$_{16}$H$_{16}$N$_2$O$_5$: C, 60.75; H, 5.10; N, 8.85. Found: C, 60.65; H, 5.15; N, 8.85. MS FAB (+)M+ = 317 (M + 1).

2(S) Methyl 2-methyl-[6-benzyl-(3-benzyloxycarbonyl-amino)-1,2-dihydro-2-oxo-1-pyridyl]-acetate (49h), was prepared by the method used in the preparation of compound **49a** to afford (58%) an oil; $[\alpha]_D^{25}$ -25.0° (c 1, CH$_2$Cl$_2$); IR (KBr) 3381, 1736, 1650, 1604, 1513, 1218, 1190, 1068; ^{1}H NMR (CDCl$_3$) δ 7.97 (1H, d), 7.78 (1H, s), 7.4-7.14 (10H, m), 6.17 (1H, d), 5.19 (2H, s), 4.64 (1H, q), 3.98 (2H, s), 3.62 (3H, s), 1.31 (3H, d).

Methyl [6-benzyl-1,2-dihydro-2-oxo-3-(2-phenylethoxy)-carbonylamino-1-pyridyl]acetate (49i), was isolated (88%) as a colorless solid: mp. 130-133°C; IR (KBr) 3363, 1746, 1732, 1651, 1604, 1515, 1368, 1231, 1212, 1185; ^{1}H NMR (CDCl$_3$) δ 8.00 (1H, d, J = 7.0), 7.68 (1H, s), 7.36-7.10 (10H, m), 6.15 (1H, d, J = 7.6), 4.7 (2H, s), 4.38 (2H, t, J = 7.0), 3.88 (2H, s), 3.67 (3H, s), 2.98 (2H, t, J = 7).

49 → 50
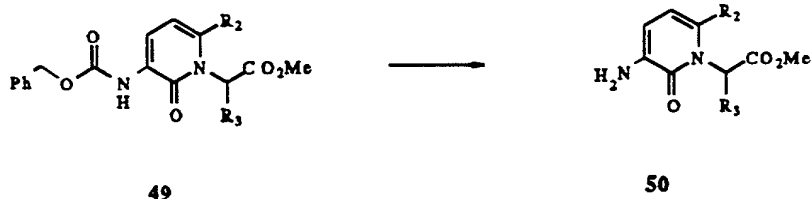
2(S) Methyl 2[3-amino-1,2-dihydro-2-oxo-1-pyridyl]propionate (50a). A mixture of 2(S) methyl-2[3-benzyloxycarbonylamino-1,2-dihydro-2-oxo-1-pyridyl]propionate (49a) (2.75g, 8.33mmol), methanol (100ml), and 10% palladium on carbon (300mg) was stirred under an atmosphere of hydrogen for 30min. The mixture was filtered and concentrated to afford 1.63g (100%) of a colorless solid: ^{1}H NMR (d$_6$-DMSO) δ 8.35 (1H, brs), 7.46 (1H, d), 7.22 (1H,d), 6.29 (1H, t), 5.22 (1H, q), 3.63 (3H, s), 1.55 (3H, d).

The following compounds were prepared in a similar manner:

Methyl [3-amino-6-benzyl-1,2-dihydro-2-oxo-1-pyridyl]acetate (50b). 100% yield as a grey solid: mp. 134-6°C; IR (KBr) 3418, 3312, 1723, 1658, 1596, 1548, 1435, 1290, 1245, 1011; ^{1}H NMR (d$_6$-DMSO) δ 7.25 (5H, m), 6.45 (1H, d, J = 7.4), 5.92 (1H, d, J = 7.4), 5.00 (2H, s), 4.63 (2H, s), 3.88 (2H, s), 3.51 (3H, s).

Methyl [3-amino-1,2-dihydro-2-oxo-6-phenethyl-1-pyridyl]acetate (50c). 99% yield as a viscous oil: IR (KBr) 3456, 341, 2953, 1745, 1649, 1600, 1548, 1219; ^{1}H NMR (CDCl$_3$) δ 7.25 (5H, m), 6.51 (1H, d, J = 7.4), 5.92 (1H, d, J = 7.4), 4.79 (2H, s), 3.77 (3H, s), 2.80 (4H, m).

Methyl[3-amino-6-butyl-1,2-dihydro-2-oxo-1-pyridyl]acetate (50d). 97% as a brown solid: mp. 75-7°C; IR (KBr) 3437, 3342, 2955, 1745, 1655, 1609, 1550, 1432, 1301, 1222, 1200; ^{1}H NMR (CDCl$_3$) δ 6.53 (1H, d, J = 6.8), 5.93 (1H, d, J = 6.8), 4.81 (2H, s), 3.77 (3H, s), 2.44 (2H, t), 1.45 (4H, m), 0.93 (3H, t).

Methyl[3-amino-1,2-dihydro-6-methyl-2-oxo-1-pyridyl]acetate (50e), was isolated (100%) as a colorless crystalline solid: mp. 87-9°C; IR (KBr) 3442, 3326, 1735, 1647, 1600, 1549, 1434, 1407, 1383, 1366, 1225, 1209; ^{1}H NMR (d$_6$-DMSO) δ 6.40 (1H, d, J = 7.3), 5.93 (1H, d, J = 7.3), 4.86 (2H, s), 4.79 (2H, s), 3.67 (3H, s), 2.15 (3H, s).

Methyl[3-amino-1,2-dihydro-2-oxo-6-phenyl-1-pyridyl]acetate (50f), was isolated (86%) as a grey solid: mp. 207-9°C; IR (KBr) 3473, 3345, 1750, 1644, 1600, 1536, 1443, 1366, 1309, 1212, 1184, 1156; ^{1}H NMR (d$_6$-DMSO) δ 7.30 (5H, m), 6.54 (1H, d), 6.03 (1H, d), 5.25 (2H, s), 4.49 (2H, s), 3.61 (3H, s).

Methyl[3-amino-1,2-dihydro-2-oxo-1-pyridyl]acetate (50g), was obtained as a colorless oil and used immediately in the next step.

2(S) Methyl 2-methyl-[3-amino-6-benzyl-1,2-dihydro-2-oxo-1-pyridyl]acetate (50h), was isolated (69%) as a colorless oil: IR (film) 3354, 1743, 1646, 1600, 1548, 1494, 1455, 1309, 1268, 1227, 113; ^{1}H NMR (C$_6$D$_6$) δ 7.29-6.76 (5H, m), 5.86 (1H, d, J = 7.2), 5.51 (1H, d, J = 7.2), 4.43 (1H, q, J = 6.7), 3.69 (2H, s), 3.41 (2H, s), 3.36 (3H, s), 1.43 (3H, d, J = 6.7).

$$50 \longrightarrow 51$$
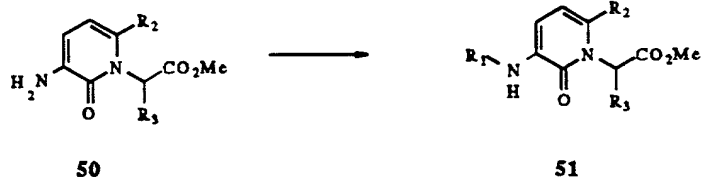
		R_1	R_2	R_3
	(a)	$Ph(CH_2)_2CO$	H	(S)Me
	(b)	$Ph(CH_2)_2CO$	CH_2Ph	H
5	(c)	$Ph(CH_2)_2CO$	$(CH_2)_2Ph$	H
	(d)	$Ph(CH_2)_2CO$	nBu	H
	(e)	$Ph(CH_2)_2CO$	Me	H
	(f)	$Ph(CH_2)_2CO$	Ph	H
	(g)	$Ph(CH_2)_2CO$	H	H
10	(h)	$Ph(CH_2)_2CO$	CH_2Ph	(S)-Me or (R,S)-Me
	(i)	AcTyr	CH_2Ph	H
	(j)	$Ph(CH_2)_2SO_2$	CH_2Ph	H
	(k)	$Ph(CH_2)_2OCO$	CH_2Ph	H
15	(l)	$Ph(CH_2)_3CO$	CH_2Ph	H

2(S) **Methyl 2-[1,2-dihydro-2-oxo-3-(3-phenylpropionyl)**
amino-1-pyridyl]- propionate (51a). 3-Phenylpropionyl
chloride (1.5g, 9mmol) was added dropwise to a stirred
mixture of 2S methyl-2-[3-amino-1,2-dihydro-2-oxo-1-
pyridyl]propionate (**50a**) (1.63g, 8.33mmol), dioxane
(60ml), water (15ml) and sodium bicarbonate (1.54g,
16.7mmol). The mixture was kept for 1h then extracted
with ethyl acetate. The extracts were washed with
aqueous sodium bicarbonate, dried (MgSO₄) and
concentrated. The resulting red oil was purified by
flash chromatography to afford 2.54g (93%) of an oil:

$[\alpha]_D^{20}$ -68°C (1, CH_2Cl_2); IR (CH_2Cl_2) 3369, 1747, 1690, 1650, 1602, 1512, 1267, 1260, 1217; ^{1}H NMR ($CDCl_3$) δ 8.41 (1H, dd), 8.36 (1H, s), 7.24 (5H, m), 7.02 (1H, dd), 6.32 (1H, t), 5.44 (1H, q), 3.75 (3H, s), 3.03 (2H, t), 2.70 (2H, t), 1.66 (3H, d). FAB M+ = 329 (M + 1), 197, 165, 131, 110, 91.

The following compounds were prepared in a similar manner:

Methyl [6-benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl]-acetate (51b), was isolated (93%) as crystals: mp. 95-7°C; IR (KBr) 3265, 1747, 1686, 1642, 1590, 1563, 1511, 1454, 1401, 1220, 1183, 1133; ^{1}H NMR ($CDCl_3$) δ 8.39 (1H, d, J = 7.7), 8.27 (1H, s), 7.21 (10H, m), 6.17 (1H, d, J = 7.7), 4.70 (2H, s), 3.89 (2H, s), 3.67 (3H, s), 3.02 (2H, m), 2.70 (2H, m).

Methyl [1,2-dihydro-2-oxo-6-phenethyl-3-(3-phenylpropionyl)amino-1-pyridyl]-acetate (51c), was isolated (81%) as colorless crystals: mp. 105-8°C; IR (KBr) 3378, 1746, 1680, 1646, 1597, 1517, 1221; ^{1}H NMR ($CDCl_3$) δ 8.34 (1H, d, J = 7.7), 8.25 (1H, s), 7.23 (10H, m), 6.11 (1H, d, J = 7.7), 4.77 (2H, s), 3.78 (3H, s), 2.88 (8H, m).

Methyl [6-butyl-1,2-dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl]-acetate (51d), was isolated (88%) as colorless crystals: mp. 84-5°C; IR (KBr) 3345, 2958, 2930, 1756, 1693, 1650, 1602, 1510, 1227, 1180, 1137; ^{1}H NMR ($CDCl_3$) δ 8.34 (1H, d, J = 7.7), 8.22 (1H, s), 7.26 (5H, m), 6.12 (1H, d, J = 7.7), 4.80 (2H, s), 3.79 (3H, s), 3.03 (2H, t), 2.68 (2H, t), 2.50 (2H, t), 1.46 (4H, m), 0.95 (3H, t).

Methyl [1,2-dihydro-6-methyl-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl]-acetate (51e), was isolated (100%) as a pale yellow oil: IR (film) 3264, 1745, 1691, 1644, 1587, 1566, 1518, 1495, 1400, 1215, 1183, 1136; ^{1}H NMR (CDCl$_3$) δ 8.33 (1H, d, J = 7.6), 7.26 (5H, m), 6.13 (1H, d, J = 7.6), 4.83 (2H, s), 3.79 (3H, s), 3.03 (2H, m), 2.69 (2H, m), 2.28 (3H, s).

Methyl [1,2-dihydro-2-oxo-6-phenyl-3-(3-phenylpropionyl)amino-1-pyridyl]-acetate (51f), was isolated (99%) as a pale yellow oil: IR (film) 3365, 3299, 1751, 1689, 1643, 1600, 1563, 1519, 1493, 1419, 1370, 1224; ^{1}H NMR (CDCl$_3$) δ 8.46 (1H, d, J = 7.7), 8.32 (1H, s), 7.32 (10H, m), 6.24 (2H, d, J = 7.7), 4.57 (2H, s), 3.73 (3H, s), 3.06 (2H, m), 2.72 (2H, m).

Methyl [1,2-dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl]-acetate (51g), was isolated (81%) as an oil: IR (film) 3330, 1753, 1689, 1650, 1600, 1560, 1517, 1374, 1225, 1208; ^{1}H NMR (CDCl$_3$) δ 8.43 (1H, dd, J = 7.4, 1.7), 8.33 (1H, s), 7.28 (5H, m), 6.92 (1H, dd, J = 6.9, 1.7), 6.29 (1H, t), 4.67 (2H, s), 3.79 (3H, s), 3.04 (2H, m), 2.70 (2H, m). MS FAB (+) M + = 315 (M + 1).

2(S) Methyl 2-methyl-[6-benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl]-acetate (51h), was isolated (93%) as a colorless oil; $[\alpha]_D^{30}$ -19° (c 1, CH$_2$Cl$_2$); IR (film) 3354, 3313, 3028, 2950, 1745, 1687, 1645, 1600, 1567, 1514, 1454, 1225; ^{1}H NMR (CDCl$_3$) δ 8.35 (1H, d, J = 7.5), 8.26 (1H, s), 7.27 (10H, m), 6.20 (1H, d, J = 7.5), 4.65 (1H, q, J = 6.8), 3.99 (2H, s), 3.71 (3H, s), 3.03 (2H, m), 2.68 (2H, m), 1.31 (3H, d, J = 6.8).

Methyl [3-(N-acetyl-O-benzyl-L-tyrosine)amino-6-benzyl-1,2-dihydro-2-oxo-pyridyl]acetate (51i). A stirred mixture of methyl [3-amino-6-benzyl-1,2-dihydro-2-oxo-1-pyridyl]acetate (100mg, 0.367mmol), Boc-Tyr(Bn)-OH (136mg, 0.367mmol), dimethylformamide (1ml), diisopropylethylamine (0.25ml, 1.468mmol) and 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (118mg, 0.367mmol) was kept overnight at room temperature. The mixture was diluted with ethyl acetate, washed twice with 1M hydrochloric acid, twice with aqueous sodium bicarbonate, once with brine, then dried (MgSO$_4$) and concentrated. The residue was purified by flash chromatography (10% ethyl acetate/dichloromethane) to afford a 162mg (70%) of a colorless oil. The oil (160mg, 0.255mmol) was dissolved in dichloromethane (1ml) and treated with trifluoroacetic acid (1ml) at 0°C. The resulting solution was allowed to reach room temperature during 40min then evaporated to dryness at 30°C. The residue was dissolved in dichloromethane then evaporated to dryness again. This procedure was repeated three times. The residue was dissolved in pyridine (0.5ml) and treated with acetic anhydride (0.03ml, 0.3mmol) at 0°C. The resulting mixture was allowed to reach room temperature and kept for 3.5h. It was diluted with ethyl acetate, washed twice with 1M hydrochloric acid, twice with aqueous sodium bicarbonate, dried (MgSO$_4$) and concentrated to afford 128mg (86%) of a colorless oil: IR (film) 3290, 1751, 1649, 1602, 1568, 1513, 1455, 1438, 1375, 1224, 1179; ^{1}H NMR (CDCl$_3$) δ 8.78 (1H, s), 8.33 (1H, d, J = 7.6), 7.33 (8H, m), 7.11 (4H, m), 6.86 (2H, d, J = 8.5), 6.47 (1H, d, J = 7.6), 6.12 (1H, d, J = 7.6), 4.99 (2H, s), 4.85 (1H, m), 4.69 (2H, s), 3.87 (2H, s), 3.62 (3H, s), 3.08 (2H, m), 1.96 (3H, s).

Methyl[6-benzyl-1,2-dihydro-2-oxo-3-(2-phenylethanesulphonyl)amino-1-pyridyl]-acetate (51j).
2-Phenylethanesulphonyl chloride (Zhong et al., _J. Am. Chem. Soc._, 113, pp. 2259-63 (1991)) was added to a
stirred mixture of methyl [3-amino-6-benzyl-2-oxo-1,2-dihydro-1-pyridyl]-acetate (**49b**) (1.0g, 3.67mmol),
dichloromethane (15ml) and triethylamine (1.0ml, 7.34mmol). The mixture was kept overnight then poured
into ethyl acetate. The resulting mixture was washed
twice with aqueous sodium bicarbonate, three times with
1M hydrochloric acid, then brine. It was dried ($MgSO_4$)
and concentrated. The resulting pale brown solid was
purified by flash chromatography (10% ethyl acetate/
dichloromethane) to afford 1.25g (77%) of a pale yellow
solid: m.p. 92-4°C; IR (KBr) 3181, 1737, 1646, 1595,
1565, 1454, 1241, 1220, 1150; ^{1}H NMR ($CDCl_3$) δ 7.53 (1H,
d, J = 7.5), 7.29 (10H, m), 6.10 (1H, d, J = 7.5), 4.75
(2H, s), 3.89 (2H, s), 3.67 (3H, s), 3.34 (2H, m), 3.14
(2H, m).

Methyl [6-benzyl-1,2-dihydro-2-oxo-3-(4-phenylbutyryl)amino-1-pyridyl]-acetate (51l), was isolated (74%) as
colorless crystals: mp. 93-95°C; IR (KBr) 3285, 1747,
1683, 1642, 1591, 1563, 1512, 1455, 1220, 1181; ^{1}H NMR
($CDCl_3$) δ 8.39 (1H, d, J = 7.6), 8.24 (1H, s), 7.2 (10H,
m), 6.18 (1H, d, J = 7.6), 4.7 (2H, s), 3.90 (2H, s),
3.67 (3H, s), 2.69 (2H, t), 2.40 (2H, t), 2.04 (2H, m).

51   52

2(S) 2-[1,2-Dihydro-2-oxo-3-(3-phenylpropionyl)amino)-1-pyridyl]propionic acid (52a). 1M Sodium hydroxide (15ml, 15mmol) was added to a stirred solution of 2(S) methyl 2-[1,2-dihydro-2-oxo-3(3-phenylpropionyl)amino-

5 1-pyridyl]propionate (**51a**) (2.39g, 7.3mmol) in methanol (30ml) at 0°C. The mixture was kept at this temperature for 2h, acidified with 1M hydrochloric acid (15.1ml) and extracted with ethyl acetate. The extracts were washed with brine, dried (MgSO$_4$) and

10 concentrated to afford 1.98g (87%) of a colorless solid: $[\alpha]_D^{20}$ -75° (1, CH$_2$Cl$_2$); IR (KBr) 3301, 1724, 1693, 1637, 1563, 1523, 1453, 1233, 1216, 765; ^{1}H NMR (CDCl$_3$) δ 8.47 (2H, m), 7.20 (5H, m), 7.03 (1H, d), 6.36 (1H, t), 5.35 (1H, q), 3.01 (2H, m), 2.70 (2H, m), 1.69

15 (3H, m).

The following compounds were prepared in a similar manner:

[6-Benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl]acetic acid (52b), was isolated (100%) as a

20 pale amber oil: IR (film) 3291, 1738, 1686, 1644, 1591, 1554, 1519, 1496, 1454, 1403, 1215, 1182; ^{1}H NMR (CDCl$_3$) δ 8.44 (1H, d, J = 7.8), 8.4 (1H, s), 7.21 (10H, m), 6.19 (1H, d, J = 7.8), 4.71 (2H, s), 3.90 (2H, s), 2.99 (2H, m), 2.71 (2H, m).

25 **[1,2-Dihydro-2-oxo-6-phenethyl-3-(3-phenylpropionyl)amino-1-pyridyl]acetic acid (52c)**, was isolated (94%) as a beige solid: mp. 214-6°C; IR (KBr) 3289, 1740, 1680, 1640; ^{1}H NMR (d$_6$-DMSO) δ 9.24 (1H, s), 8.14 (1H, d, J = 7.7), 7.22 (10H, m), 6.11 (1H, d, J = 7.8), 4.78

30 (2H, s), 2.81 (8H, m).

[6-Butyl-1,2-dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl]acetic acid (52d), was isolated (99%) as a pale brown solid: mp. 132-4°C; IR (KBr) 3286, 1739, 1676, 1641, 1584, 1555, 1535, 1455, 1414, 1249, 1227, 1204; ^{1}H NMR (CDCl$_3$) δ 8.42 (1H, d, J = 7.8), 8.37 (1H, s), 7.24 (5H, m), 6.19 (1H, d, J = 7.8), 4.82 (2H, s), 3.55 (1H, s), 3.00 (2H, t), 2.67 (2H, t), 2.53 (2H, t), 1.41 (4H, m), 0.94 (3H, t).

[1,2-Dihydro-6-methyl-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl]acetic acid (52e), was isolated as a solid (100%): mp. 159-61°C; IR (KBr) 3335, 1731, 1686, 1642, 1536, 1516, 1430, 1420, 1401, 1222, 1195; ^{1}H NMR (d$_6$-DMSO) δ 9.21 (1H, s), 8.13 (1H, d, J = 7.6), 7.20 (5H, m), 6.15 (1H, d, J = 7.6), 4.77 (2H, s), 2.87 (2H, m), 2.70 (2H, m), 2.25 (3H, s).

[1,2-Dihydro-2-oxo-6-phenyl-3-(3-phenylpropionyl)amino-1-pyridyl]acetic acid (52f), was isolated (100%) as a pale yellow foam: IR (KBr) 3271, 1747, 1683, 1634, 1580, 1536, 1490, 1406, 1392, 1365, 1235, 1219; ^{1}H NMR (CDCl$_3$) δ 8.52 (1H, d, J = 7.7), 7.31 (10H, m), 6.48 (2H, s), 6.30 (1H, d, J 7.7), 4.60 (2H, s), 3.03 (2H, m), 2.71 (2H, m).

[1,2-Dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl]acetic acid (52g), was isolated (94%) as a colorless solid: mp. 195-7°C; IR (KBr) 3324, 1724, 1693, 1644, 1569, 1555, 1512, 1427, 1370, 1240; ^{1}H NMR (d$_6$-DMSO) δ 9.31 (1H, s), 8.23 (1H, d, J = 6.8), 7.36 (1H, dd, J = 6.8, 1.71), 7.25 (5H, m), 6.25 (1H, t), 4.66 (2H, s), 2.84 (4H, m).

2(R,S) 2-[6-Benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl]-propionic acid (52h),

was prepared by hydrolysis of compound **51h** in aqueous
tetrahydrofuran during 5h at 40°C to afford (95%) as a
yellow oil: IR (film) 3330, 1734, 1686, 1643, 1600,
1587, 1553, 1524, 1498, 1208; ^{1}H NMR (d_6-DMSO) δ 9.29
(1H, s), 8.18 (1H, d, J = 7.6), 7.21 (10H, m), 6.22
(1H, d, J = 7.6), 4.82 (1H, q, J = 6.6), 4.08 (2H, m),
2.76 (4H, m), 1.05 (3H, d, J = 6.6).

**[3-(Acetyl-Tyr(Bn))amino-6-benzyl-1,2-dihydro-2-oxo-1-
pyridyl]acetic acid (52i)**, was isolated (93%) as a
foam: IR (KBr) 3302, 1731, 1646, 1603, 1562, 1512,
1454, 1428, 1379, 1231, 1178; ^{1}H NMR (CDCl$_3$) δ 9.48 (1H,
s), 8.36 (1H, d, J = 7.6), 7.30 (8H, m), 7.10 (2H, m),
6.85 (2H, d, J = 8.3), 6.91 (2H, d, J = 8.3), 6.71 (1H,
d, J 7.6), 4.95 (1H, m), 4.90 (2H, s), 4.68 (2H, s),
3.92 (2H, s), 3.17-2.83 (2H, m), 1.92 (3H, s).

**[6-Benzyl-1,2-dihydro-2-oxo-3-(2-
phenylethanesulphonyl)amino-1-pyridyl]acetic acid
(52j)**, was isolated (100%) as a colorless solid: mp.
165-7°C;   IR (KBr) 3174, 1760, 1646, 1593, 1567, 1497,
1453, 1424, 1326, 1225, 1140, 1127; ^{1}H NMR (d_6-DMSO) δ
13.09 (1H, s), 9.08 (1H, s), 7.30 (11H, m), 6.02 (1H,
d), 4.68 (2H, s), 4.99 (2H, s), 3.29 (2H, m), 3.03 (2H,
m).

**[6-Benzyl-1,2-dihydro-2-oxo-3-(2-phenylethoxy)
carbonylamino-1-pyridyl]acetic acid (52k)**, was prepared
(70%) by hydrolysis of compound **49i** during 1h at 60°C:
IR (CH$_2$Cl$_2$) 1797, 1689, 1649, 1601, 1512, 734; ^{1}H NMR
(CDCl$_3$) δ 8.39 (1H, s), 8.03 (1H, d), 7.81 (1H, s),
7.33-7.07 (10H, m), 6.13 (1H, d, J = 7.8), 4.72 (2H,
s), 4.33 (2H, t, J = 7.0), 3.86 (2H, s), 2.93 (2H, t, J
= 7.0).

[6-Benzyl-1,2-dihydro-2-oxo-3-(4-phenylbutyryl)amino-1-pyridyl]acetic acid (521), was isolated (100%) as a white foam: m.p. 159-161°C; IR (KBr) 3373-3310, 1787, 1726, 1691, 1649, 1599, 1567, 1517, 1367, 1215; ^{1}H NMR (CDCl$_3$) δ 8.43 (1H, d, J = 7.7), 8.25 (1H, s), 7.37-7.09 (10H, m), 6.21 (1H, d, J = 7.7), 4.73 (2H, s), 4.15 (3H, s), 3.91 (2H, s), 2.67 (2H, t), 2.39 (2H, t), 2.02 (2H, m).
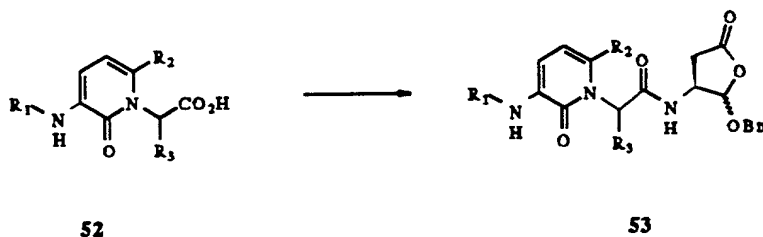
52   **53**

2(S), N-3(S) 2-[1,2-Dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl]-N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)propionamide (53a). Tri-n-butyltin hydride (1.7ml, 6.3mmol) was added dropwise to a stirred mixture of 2(S)-2-[1,2-dihydro-2-oxo-3(3-phenylpropionyl)amino-1-pyridyl]propionic acid **(52a)** (1.1g, 3.49mmol), 3(S), 2(R,S) 3-allyloxycarbonylamino-2-benzyloxy-5-oxotetrahydrofuran (1.02g, 3.49mmol; Chapman, Biorg. Med. Chem. Lett., 2, pp. 613-18 (1992)), bis(triphenylphosphine)palladium (II) chloride (55mg), dichloromethane (35ml) and dimethylformamide (1ml). The resulting mixture was stirred for 5 min. then 1-hydroxybenzotriazole (946mg, 7mmol) was added. The mixture was cooled to 0°C before the addition of 1-(3-dimethylaminopropyl)-2-ethylcarbodiimide hydrochloride (740mg, 3.84mmol). The mixture was kept overnight at room temperature then poured into ethyl acetate. The mixture was washed twice with 1M hydrochloric acid, twice with aqueous sodium bicarbonate, then brine. The mixture was dried (MgSO$_4$)

and concentrated. The residue was triturated with pentane. The remaining solid was purified by flash chromatography (40-60% ethyl acetate/hexane) to afford 1.28g (73%) of colorless solid: IR (KBr) 1796, 1692, 1647, 1595, 1557, 1512, 1119; ^{1}H NMR (d$_6$-DMSO) δ 9.28, 9.26 (1H, 2 x s), 8.77, 8.69 (1H, 2 x d), 8.24, 8.20 (1H, 2 x dd), 7.20 (11H, m), 6.31, 6.26 (1H, 2 x t), 5.65 (0.5H, d), 5.46 (0.5H, d), 5.41, 5.28 (1H, 2 x q), 4.7 (2.5H, m), 4.24 (0.5H, t), 3.24 (2H, m), 2.80 (4H, m), 1.51, 1.46 (3H, 2 x d).

The following compounds were prepared in a similar manner:

N(3(S)) 2[6-Benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl]-N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)acetamide (53b), was obtained (86%) as a foam: IR (KBr) 3345, 3297, 1807, 1791, 1688, 1679, 1650, 1602, 1554, 1525, 1497, 1453, 1372, 1257, 1119; ^{1}H NMR (d$_6$-DMSO) δ 9.25 (0.5H, s), 9.23 (0.5H, s), 8.75 (0.5H, d, J = 6.5), 8.67 (0.5H, d, J = 7.4), 8.18 (1H, 2d), 7.21 (15H, m), 6.07 (1H, 2d), 5.65 (0.5H, d, J = 5.0), 5.38 (0.5H, s), 4.83-4.45 (4.5H, m), 4.19 (0.5H, m), 3.94, 3.83 (2H, m), 3.10-2.31 (6H, m).

N(3(S)) 2[1,2-Dihydro-2-oxo-6-phenethyl-3-(3-phenylpropionyl)amino-1-pyridyl]-N-(2-benzyloxy-5-oxotetrahydrofuran-4-yl)acetamide (53c), was obtained (74%) as a mixture of anomers: ^{1}H NMR (d$_6$-DMSO) δ 9.71 (1H, d), 9.41 (0.5H, d), 9.25 (0.5H, d), 8.64 (1H, d, J = 7.7), 7.75 (15H, m), 6.61 (1H, 2d), 6.11 (0.5H, d), 5.93 (0.5H, s), 5.17 (5H, m), 4.77 (0.5H, m), 3.68-2.94 (2H, m), 3.32 (8H, m).

N(3(*S*)) 2[6-Butyl-1,2-dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl]-N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)acetamide (53d), was obtained (74%) as a mixture of anomers: IR (KBr) 3300, 1791, 1689, 1645, 1597, 1566, 1546, 1514, 1454, 1417, 1378; ^{1}H NMR (CDCl$_3$) δ 8.38 (1H, d, *J* = 7.7), 8.13 (1H, s), 7.30 (10H, m), 6.18 (1H, t), 5.47 (0.5H, d, *J* = 5.2), 5.43 (0.5H, s), 4.75 (4.5H, m), 4.38 (0.5H, m), 3.08-2.35 (8H, m), 1.43 (4H, m), 0.95 (3H, t).

N(3(*S*)) 2[1,2-Dihydro-6-methyl-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl]-N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)acetamide (53e), was obtained (67%) as a mixture of anomers: IR (KBr) 3282, 1774, 1667, 1651, 1596, 1561, 1556, 1498, 1265, 1254, 1236, 1199, 1143; ^{1}H NMR (d$_6$-DMSO) δ 9.17 and 9.15 (1H, 2 x s), 8.89 (0.5H, d, *J* = 6.5), 8.73 (0.5H, d, *J* = 7.4), 7.25 (10H, m), 6.13 (1H, t), 5.64 (0.5H, d, *J* = 5.0), 5.45 (0.5H, s), 4.89-4.61 (4.5H, m), 4.26 (0.5H, m), 3.17-2.36 (6H, m), 2.23 and 2.15 (3H, 2s).

N(3(*S*)) 2-[1,2-Dihydro-2-oxo-6-phenyl-3(3-phenylpropionyl)amino-1-pyridyl]-N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)acetamide (53f), was obtained (73%) as a mixture of anomers: IR (KBr) 3296, 1792, 1691, 1643, 1595, 1561, 1514, 1489, 1453, 1420, 1373, 1230, 1118; ^{1}H NMR (d$_6$-DMSO) δ 9.40, 9.36 (1H, 2s), 8.70 (0.5H, d, *J* = 7.6), 8.52 (0.5H, d, *J* = 7.5), 8.29 (1H, dd), 7.25 (15H, m), 6.20 (1H, d, *J* = 7.6), 5.61 (0.5H, d, *J* = 5.0), 5.28 (0.5H, s), 4.78-4.20 (5H, m), 3.12-2.24 (6H, m).

N(3(*S*)) 2-[1,2-Dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl]-N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)acetamide (53g), was obtained (70%) as a mixture of

anomers: IR (KBr) 3336, 3290, 1791, 1691, 1646, 1595, 1582, 1556, 1518, 1454, 1376, 1351, 1150, 1122; ^{1}H NMR (d$_6$-DMSO) δ 9.26 (1H, 2s), 8.86 (0.5H, d, J = 6.4), 8.67 (0.5H, d, J = 7.5), 8.23 (1H, m), 7.40-7.13 (11H, m), 6.24 (1H, 2t, J = 7.2), 5.61 (0.5H, d, J = 5.0), 5.44 (0.5H, s), 4.83-4.59 (2.5H, m), 4.25 (0.5H, m), 3.15-2.34 (2H, m), 2.91-2.70 (4H, m). Anal. Calc. for C$_{27}$H$_{27}$N$_3$O$_6$ H$_2$O: C, 63.90; H, 5.76; N, 8.28. Found: C 63.70; H, 5.68; N, 8.22. MS FAB M$^+$ = 490 (M + 1).

2(R, S), N(3(S)) 2-[6-Benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl]-N(2-benzyloxy-5-oxotetrahydrofuran-3-yl)propionamide (53h), was obtained (89%) as a mixture of diastereomers. Data is given for a single diastereomer: IR (film) 3356, 1788, 1677, 1645, 1602, 1517, 1455, 1377, 1203, 1167, 1120; ^{1}H NMR (CDCl$_3$) δ 8.34 (1H, d, J = 7.6), 8.19 (1H, s), 7.38-7.13 (10H, m), 6.26 (1H, d, J = 7.6), 5.58 (1H, t), 5.31, 5.24 (1H, 2 x s), 4.62 (2H, 2q), 4.60 (1H, m), 4.27 (1H, m), 2.98, 2.68 (4H, 2m), 3.0-2.0 (2H, m), 1.42 (3H, d).

N(3(S)) 2-[6-Benzyl-1,2-dihydro-2-oxo-3-(N-acetyl-O-benzyltyrosinyl)amino-1-pyridyl]-N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)acetamide (53i), was obtained (76%) as a mixture of anomers: IR (KBr) 1794, 1698, 1651, 1612, 1514, 1454, 1374, 1247, 1177, 1126; ^{1}H NMR (d$_6$-DMSO) δ 9.34, 9.31 (2 x 0.5H, 2s), 8.71 (1H, 2d), 8.38 (1H, m), 8.17 (1H, d), 7.48-6.88 (19H, m), 6.08 (1H, 2d), 5.65 (0.5H, d, J = 5.0), 5.40 (0.5H, s), 5.04 (2H, s), 4.68 (5.5H, m), 4.15 (0.5H, m), 3.95, 3.84 (2H, s + abq), 3.20-2.40 (4H, m), 1.78 (3H, s).

N(3(*S*)) 2-[6-Benzyl-1,2-dihydro-2-oxo-3-(2-phenylethanesulphonyl)amino-1-pyridyl]-*N*-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)acetamide (53j), was obtained (78%) as a mixture of anomers: IR (KBr) 3344, 1792, 1691, 1647, 1599, 1566, 1454, 1365, 1150, 1121, 973; ^{1}H NMR (d$_6$-DMSO) δ 9.02, 8.99 (1H, 2s), 8.80 (0.5H, d, *J* = 6.4), 8.70 (0.5H, d, *J* = 7.4), 7.26 (15H, m), 6.00 (1H, dd), 5.63 (0.5H, d, *J* = 5.0), 5.39 (0.5H, s), 4.68 (4.5H, m), 4.18 (0.5H, m), 3.90 (2H, m), 3.30-2.30 (6H, m).

N(3(*S*)) 2-[6-Benzyl-1,2-dihydro-2-oxo-3-(2-phenylethoxy)carbonylamino-1-pyridyl]-*N*-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)acetamide (53k), was obtained (78%) as a mixture of anomers: IR (KBr) 3386, 1794, 1726, 1650, 1603, 1518, 1366, 1214, 699; ^{1}H NMR (CDCl$_3$) δ 8.03 (1H, bd), 7.63, 7.61 (1H, 2 x s), 7.34-7.04 (15H, m), 6.21, 6.18 (1H, 2d), 5.44 (0.5H, d, *J* = 5.4), 5.37 (0.5H, s), 4.85, 4.83 (1H, 2d, *J* = 11.6, 11.5), 4.61-4.48, 4.32 (4H, 2m), 4.4 (2H, t), 4.08, 4.03 (2H, 2bs), 3.07-2.78 (3H, m), 2.47-2.30 (1H, m).

N(3(*S*)) 2-[6-Benzyl-1,2-dihydro-2-oxo-3-(4-phenylbutyryl)amino-1-pyridyl]-*N*-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)acetamide (53l), was obtained (86%) as a colorless oil: IR (CH$_2$Cl$_2$) 1797, 1689, 1649, 1601, 1512, 734; ^{1}H NMR (CDCl$_3$) δ 8.42, 8.40 (1H, 2d, *J* = 7.6), 7.35-7.07 (15H, m), 6.21, 6.19 (1H, 2d, *J* = 7.6), 5.44 (0.5H, d), 5.37 (0.5H, s), 4.84, 4.81 (1H, 2d, *J* = 11.7, 11.4), 4.73-4.48, 4.34 (4H, 2m), 4.05 (2H, m), 3.05-2.63, 2.46-2.30 (6H, 2m), 2.01 (2H, m).
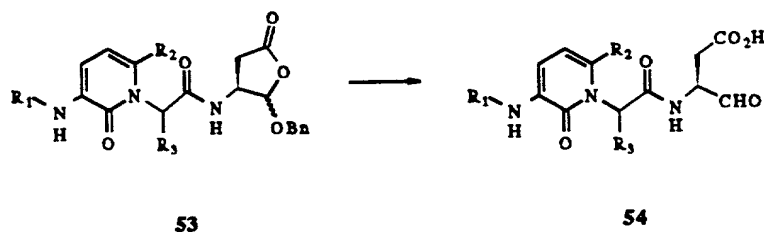
	R₁	R₂	R₃
(a)	$Ph(CH_2)_2CO$	H	$(S)Me$
(b)	$Ph(CH_2)_2CO$	CH_2Ph	H
(c)	$Ph(CH_2)_2CO$	$(CH_2)_2Ph$	H
(d)	$Ph(CH_2)_2CO$	nBu	H
(e)	$Ph(CH_2)_2CO$	Me	H
(f)	$Ph(CH_2)_2CO$	Ph	H
(g)	$Ph(CH_2)_2CO$	H	H
(h)	$Ph(CH_2)_2CO$	CH_2Ph	$(R,S)-Me$
(i)	AcTyr	CH_2Ph	H
(j)	$Ph(CH_2)_2SO_2$	CH_2Ph	H
(k)	$Ph(CH_2)_2OCO$	CH_2Ph	H
(l)	$Ph(CH_2)_3CO$	CH_2Ph	H

3(S), N(2(S)) 3-(2-(1,2-Dihydro-2-oxo-3-(3-phenylpropionylamino-1-pyridyl)-propionylamino)-4-oxobutanoic acid (54a; F). A mixture of 2(S), N(3(S)) 2-[1,2-dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl]-N(2-benzyloxy-5-oxotetrahydro-furan-3-yl)propionamide **53a** (1.28g, 2.5mmol), methanol (140ml) ethyl acetate (60ml) and 10% palladium on carbon (1.4g) was stirred under an atmosphere of hydrogen. After 2.5h more catalyst (300mg) was added and hydrogenation continued for 1h. The mixture was filtered through Celite™ and then refiltered through 0.2μM nylon filter

and concentrated. The residual oil triturated with a mixture of methanol and ether to afford 916mg (87%) of colorless crystals: mp. 198-200°C; $[\alpha]_D^{28}$ -120° (0.1, CH$_3$OH); IR (KBr) 3330, 1794, 1688, 1644, 1583, 1556, 1515, 1427; ^{1}H NMR (CD$_3$OD) δ 8.28 (1H, d), 7.35 (1H, d), 7.20 (5H, m), 6.36 (1H, t), 5.49 (1H, q), 4.59 (1H, t), 4.25 (1H, m), 2.98, 2.74 (2 x 2H, 2 x m), 2.59 (2H, m), 1.57 (3H, d). Anal. Calcd for C$_{21}$H$_{23}$N$_3$O$_6$ 0.75 H$_2$O: C, 59.08; H, 5.78; N, 9.84. Found: C 59.24; H, 5.96; N, 9.84. FAB M$^+$ = 414 (M + 1), 297, 165, 91.

The following compounds were prepared in a similar manner:

3(S) 3-(6-Benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl)acetylamino-4-oxobutanoic acid, (54b; M), was isolated (59%) as colorless crystals: mp. 115°C (decomp);. IR (KBr) 3440, 3297, 1718, 1646, 1598, 1565, 1526, 1496, 1260; ^{1}H NMR (CD$_3$OD) 8.25 (1H, d, J=7.7), 7.25 (10H, m), 6.15 (1H, 2d, each J=7.7), 4.73 (2H, 2q), 4.59 (1H, m), 4.30 (1H, m), 3.95 (2H, s), 2.98 (2H, m), 2.75 (2H, m), 2.8-2.42 (2H, m). Anal. Calcd for C$_{27}$H$_{27}$N$_3$O$_6$. 0.7 H$_2$O: C, 64.58; H, 5.70; N, 8.37. Found: C, 64.51; H, 5.63; N, 8.38. MS FAB+ M+ = 490 (M + 1).

3(S) 3-(1,2-Dihydro-2-oxo-6-phenethyl-3(3-phenyl-propionyl)amino-1-pyridyl)acetylamino-4-oxobutanoic acid (54c), was isolated (46%) as a white solid: IR (KBr) 3375, 1694, 1643, 1586, 1561, 1515, 1377, 1254, 1188, 1070; ^{1}H NMR (CD$_3$OD) 8.18 (1H, d, J=7.8), 7.22 (10H, m), 6.15 (1H, d, J=7.8), 4.75 (2H, s), 4.58 (1H, m), 4.30 (1H, m), 3.01-2.28 (10H, m); MS FAB+ M+ = 504 (M + 1).

3(*S*) 3-(6-Butyl-1,2-dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl)acetylamino-4-oxobutanoic acid (54d), was isolated (90%) as colorless crystals: m.p. 120-5°C; IR (KBr) 3315, 1784, 1679, 1644, 1589, 1561, 1556, 1520, 1415, 1379, 1186; ^{1}H NMR (CD$_3$OD) 8.22 (1H, d, J=7.8), 7.24 (5H, m), 6.22 (1H, d, J=7.8), 4.80 (2H, m), 4.60 (1H, s), 4.28 (1H, m), 2.98 (2H, m), 2.72 (2H, m), 2.58 (4H, m), 1.48 (4H, m), 0.97 (3H, t, J=7.1). Anal. Calcd for C$_{24}$H$_{29}$N$_3$O$_6$ 0.5 H$_2$O. C, 62.06; H, 6.51; N, 9.05. Found: C, 62.08; H, 6.43; N, 9.01. MS FAB+ M+ = 456 (M + 1).

3(*S*) 3-(1,2-Dihydro-6-methyl-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl)acetylamino-4-oxobutanoic acid (54e), was isolated (85%) as a colorless solid: mp. 129-138°C; IR (KBr) 327, 3294, 1710, 1695, 1682, 1554, 1525, 1379, 1272, 1240; ^{1}H NMR (CD$_3$OD) δ 8.19 (1H, d, J=7.6), 7.19, (5H, m), 6.21 (1H, d, J=7.6), 4.80 (2H, m), 4.59 (1H, m), 4.30 (1H, m), 2.98 (2H, m), 2.72 (2H, m), 2.80-2.40 (2H, m), 2.30 (3H, s). Anal. Calcd for C$_{21}$H$_{22}$N$_3$O$_6$. H$_2$O: C, 58.46; H, 5.84; N, 9.74. Found C: 58.82; H, 60.5; N, 9.42.

3(*S*) 3-(1,2-Dihydro-2-oxo-6-phenyl-3-(3-phenyl-propionyl)amino-1-pyridyl)acetylamino-4-oxobutanoic acid (54f), 73% as an off-white solid: m.p. 140°C (decomp). [α]$_D^{24}$ = -8.5° (c 0.1, MeOH). IR (KBr) 3302, 1796, 1726, 1679, 1643, 1590, 1560, 1516, 1490, 1449, 1420, 1398, 1376, 1231; ^{1}H NMR (CD$_3$OD) δ 8.36 (1H, d), 7.49-7.14 (10H, m), 6.27 (1H, dd), 4.54 (3H, m), 4.30 (1H, m), 3.0, 2.73 (2 x 2H, 2 x m), 2.7-2.29 (2H, m).

3(*S*) 3-(1,2-Dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl)acetylamino-4-oxobutanoic acid (54g; *G*), was isolated (73%) as a foam: mp. 140-5°C (decomp); IR

(KBr) 3352, 3314, 1719, 1700, 1668, 1649, 1600, 1559, 1514, 1379, 1261; ^{1}H NMR (CD$_3$OD) δ 8.32 (1H, d, J=7.5), 7.19 (6H, m), 6.34 (1H, t), 5.1-4.6 (3H, m), 4.32 (1H, m), 2.7 (6H, m). Anal. Calcd for C$_{20}$H$_{21}$N$_3$O$_6$. 0.6H$_2$O: C, 58.50, H, 5.45, N, 10.24. Found: C, 58.43, H, 5.35, N. 9.85. MS FAB+ M + = 400 (M + 1).

3(S), N(2(R,S)) 3-(2-(6-Benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl)propionylamino)-4-oxobutanoic acid (54h), was obtained (69%) as a colorless foam: m.p. 120°C; [α]$_D^{20}$ -16.0° (c, 0.11, CH$_2$Cl$_2$). IR (KBr) 3315, 1783, 1727, 1666, 1644, 1599, 1564, 1517, 1454, 1379; ^{1}H NMR (CD$_3$OD) δ 8.23 (1H, m), 7.27 (10H, m), 6.28 (1H, m), 4.84 (1H, m), 4.53 (1H, m), 4.22 (1H, m), 4.10 (2H, m), 2.96 (2H, m), 2.72 (2H, m), 2.39 (2H, m), 1.21 (3H, m). Anal. Calcd for C$_{28}$H$_{29}$N$_3$O$_6$. 1.25H$_2$O: C, 63.93, H, 6.03, N, 7.99. Found: C, 63.98, H, 5.85, N, 7.86. MS FAB (+) M+ = 504 (M + 1).

3(S) 3-(3-(2-Acetyl-L-tyrosinyl)amino-6-benzyl-1,2-dihydro-2-oxo-1-pyridyl)acetylamino-4-oxobutanoic acid (54i), was isolated (79%) as colorless crystals: mp. 193-6°C (decomp.); IR (KBr) 3284, 1644, 1599, 1565, 1519, 1455, 1429, 1407, 1375, 1267, 1251; ^{1}H NMR (d$_6$-DMSO/CDCl$_3$) δ 8.16 (1H, d, J=7.7), 7.26 (5H, m), 7.03 (2H, d, J=8.4), 6.61 (2H, d, J=8.4), 6.03 (1H, d, J=7.7), 4.58 (3H, m), 4.44 (1H, m), 4.13 (1H, m), 3.84 (2H, s), 3.07-2.30 (4H, m). Anal. Calcd for C$_{29}$H$_{30}$N$_4$O$_8$. 2H$_2$O: C, 58.19; H, 5.72; N, 9.36. Found: C, 58.11; H, 5.63; N, 9.29. MS FAB+ M+ = 563 (M + 1).

3(S) 3-(6-Benzyl-1,2-dihydro-2-oxo-3-(2-phenylethane-sulphonyl)amino-1-pydridyl)acetylamino-4-oxobutanoic acid (54j), was isolated (85%) as a colorless solid:

mp. 102-5°C; $[\alpha]_D^{23}$ -9.9° (c 0.1, MeOH); IR (KBr) 3452,
3328, 3155, 1719, 1679, 1645, 1594, 1567, 1453, 1425,
1357, 1307, 1225, 1148, 1132; ^{1}H NMR (CD$_3$OD) δ 7.52 (1H,
d, J=7.6), 7.33 (10H, m), 6.12 (1H, d, J=7.6), 4.73
(2H, m), 4.58 (1H, d, J=3.7), 4.34 (1H, m), 3.97 (2H,
s), 3.29 (2H, m), 3.08 (2H, m), 2.75-2.37 (2H, m).
Anal. Calcd for C$_{26}$H$_{27}$N$_3$O$_7$S. 1.7H$_2$O: C, 56.14; H, 5.51;
N, 7.55. Found: C, 56.20; H, 5.49; N, 7.29. MS FAB+
M+ = 526 (M + 1).

**3(S) 3-(6-Benzyl-1,2-dihydro-2-oxo-3-(2-
phenylethoxy)carbonylamino-1-pyridyl)acetylamino-4-
oxobutanoic acid (54k)**, was isolated (54%) as an off-
white solid: mp. 84-86°C; IR (KBr) 3373-3310, 1787,
1726, 1691, 1649, 1599, 1567, 1517, 1367, 1215; ^{1}H NMR
(CD$_3$OD) δ 7.93 (1H, bd, J=7.4), 7.37-7.18 (10H, m), 6.15
(1H, d, J=7.4), 4.77 (1H, d, J=3.7), 4.67 and 4.58 (2H,
2m), 4.35 (2H, t, J=6.9), 4.35 (1H, m), 3.94 (2H, s),
2.98 (2H, t, J=6.9), 2.76-2.39 (2H, m).

**3(S) 3-(6-Benzyl-1,2-dihydro-2-oxo-3-(4-
phenylbutyryl)carbonylamino-1-pyridyl)acetylamino-4-
oxobutanoic acid (541)**, was isolated (50%) as a white
solid: mp. 89-93°C; IR (KBr) 3369-3302, 1678, 1645,
1594, 1565, 1517, 1379, 1258; ^{1}H NMR (d$_4$-methanol) δ
8.25 (1H, d, J=7.6), 7.37-7.18 (10H, m), 6.15 (1H, d,
J=7.4), 4.74 (2H, m), 4.60 (1H, m), 4.30 (1H, m), 3.97
(2H, s), 2.76-2.37 (2H, m), 2.67 (2H, t), 2.45 (2H, t),
1.98 (2H, m). Anal. Calcd for C$_{28}$H$_{29}$N$_3$O$_6$. 1.5H$_2$O: C,
63.39; H, 6.08; N, 7.92. Found C: 63.69; H, 5.74; N,
7.83.

	R_1	R_2	R_3
(a)	Ph-CH₂-O	H	H
(b)	Ph-CH2-CH₂	-CH2-Ph	H
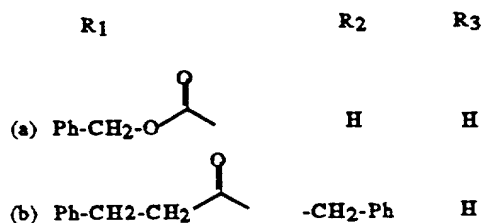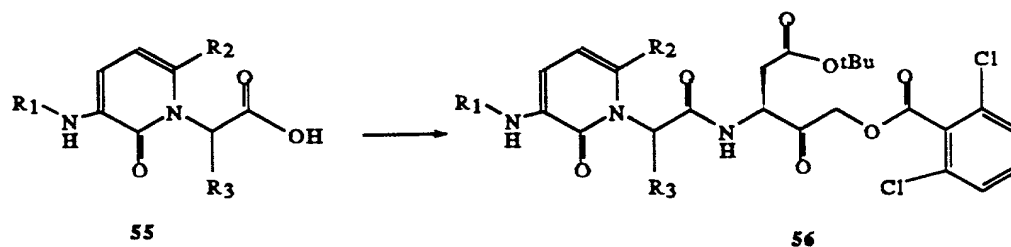
t-Butyl N-2-(3-benzyloxycarbonylamino-1,2-dihydro-2-oxo-1- pyridyl)acetyl-3-amino-5-(2,6-dichloro-benzoyloxy)-4-oxo-pentanoate (56a).   The acetic acid **(55a)** (WO 93 21213) in THF (2ml) was stirred at room

5 temperature and treated with 1-hydroxybenzotriazole (60mg, 0.448mmol) and dimethylaminopropyl-3-ethylcarbodiimide hydrochloride (47mg, 0.246mmol). After 5 mins water (2 drops) was added and stirring continued for 20 minutes.   Bis(triphenylphosphine)

10 palladium II chloride (6mg) was added followed by a solution of t-butyl 3-(allyloxycarbonylamino)-4-oxo-5-(2,6-dichlorobenzoyl-oxy)pentanoate (WO 93 16710) (103mg, 0.224mmol) in THF (1ml).   Tributyltin hydride (0.09ml, 0.336mmol) was added dropwise over 1 hour at

15 room temperature.   The mixture was stirred for a further 3 hours and poured onto ethyl acetate, washed with 1M HCl, aqueous $NaHCO_3$, brine, dried over $MgSO_4$ and concentrated *in vacuo*.   The residue was triturated with pentane and the supernatant discarded.   The remaining

20 solid was purified by flash chromatography (50% ethyl acetate/hexane) to afford the title compound 92mg (63%)

as a colorless oil: $[\alpha]_D^{26}$ -29.6° (c 1.1, CH_2Cl_2); IR
(film) 3377, 3365, 3332, 3312, 1733, 1691, 1650, 1599,
1515, 1366, 1261, 1153, 1068, 747; ^{1}H NMR (CDCl$_3$) δ 8.09
(1H, d, J = 6.8), 7.84 (1H, s), 7.58 (1H, d, J = 8.3),
7.33 (8H, m), 7.02 (1H, dd, J = 6.9, 1.7), 6.33 (1H, t,
J = 7.2), 5.20 (2H, s), 5.12 (2H, m), 4.89 (1H, dt),
4.65 (2H, m), 2.80 (2H, m), 1.38 (9H, s).

**t-Butyl N-2-(6-benzyl-1,2-dihydro-2-oxo-3-(3-
phenylpropionyl)amino-1-pyridyl)acetyl-3-amino-5-(2,6-
dichlorobenzyloxy)-4-oxo-pentanoate (56b)**, was prepared
by the method described for **(56a)** which afforded the
title compound (66%) as a colorless oil: IR (film)
3364, 3313, 1738, 1688, 1648, 1600, 1566, 1514, 1433,
1369, 1254, 1152; ^{1}H NMR (CDCl$_3$) δ 8.40 (1H, d, J 7.6),
8.30 (1H, s), 7.28 (13H, m), 6.20 (1H, d, J = 7.6),
5.12 (2H, q), 4.86 (1H, m), 4.65 (2H, q), 4.06 (2H, s),
3.07-2.61 (6H, m), 1.39 (9H, s).
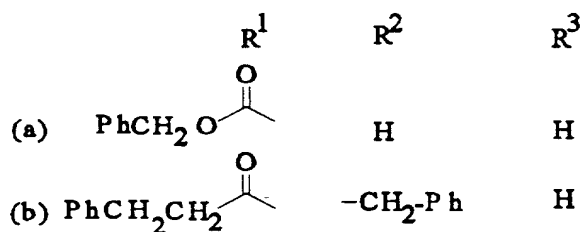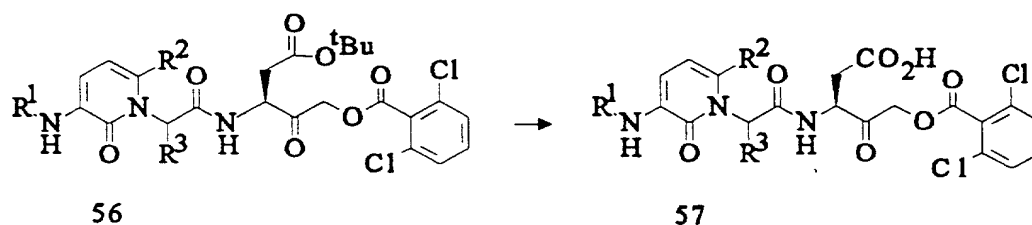
	R^1	R^2	R^3
(a)	PhCH$_2$O—C(=O)—	H	H
(b)	PhCH$_2$CH$_2$—C(=O)—	—CH$_2$-Ph	H

N-2(3-Benzyloxycarbonylamino-1,2-dihydro-2-oxo-1-pyridyl)acetyl-3-amino-5-(2,6-dichlorobenzoyloxy)-4-oxo-pentanoic acid (57a; Q). The ester (56a) (210mg, 0.356mmol) in dichloromethane (0.5ml) was cooled to 0°C and treated with trifluoroacetic acid (0.5ml), stirred and warmed to 20°C over 30 minutes. The solution was evaporated to dryness under reduced pressure, redissolved in dichloromethane and concentrated (x3). The residue was triturated with ethyl acetate and diluted with ether to afford the title compound 162mg (85%) as a colorless solid: m.p. 165-8°C (decomposition); $[\alpha]_D^{23}$ -38.8° (c 0.1, CH_3OH); IR (KBr) 3332, 3275, 1723, 1658, 1649, 1597, 1581, 1562, 1526, 1432, 1385, 1258, 1218, 1206; ^1H NMR (d_6-DMSO) δ 8.96 (1H, d, J = 7.3), 8.34 (1H, s), 7.85 (1H, dd, J = 7.3), 7.58 (3H, m), 7.35 (5H, m), 6.29 (1H, t, J = 7.3), 5.26 (2H, m), 5.15 (2H, s), 4.69 (3H, m), 2.75 (2H, m). Anal. Calcd. $C_{27}H_{23}N_3O_9Cl_2$: C, 53.66; H, 3.84; N, 6.95. Found: C, 53.36; H, 3.90; N, 6.81. M.S. (+ FAB); 604 (M^+ + 1), 285, 241, 195, 173, 149, 91.

N-2-(6-Benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl)acetyl-3-amino-5-(2,6-dichloro-benzoyloxy)-4-oxo-pentanoic acid (57b; P), was prepared by the method described for **57a** which afforded the title compound (78%) as colorless crystals: m.p. 116-120°C (decomposition); $[\alpha]_D^{26}$ -41.1° (c 0.1, CH_3OH); IR (KBr) 3299, 1739, 1715, 1689, 1666, 1645, 1598, 1563, 1518, 1432, 1209, 1151; ^1H NMR (d_6-DMSO) δ 9.24 (1H, s), 8.88 (1H, d, J = 7.6), 8.18 (1H, d, J = 7.7), 7.60 (3H, m), 7.26 (10H, m), 6.06 (1H, d, J = 7.7), 5.23 (2H, ABq), 4.69 (3H, m), 3.93 (2H, s), 2.78 (6H, m). Anal. Calcd. for $C_{35}H_{31}N_3O_8Cl_2$. H_2O: C, 59.16; H, 4.68; N, 5.91. Found: C, 59.38; H, 4.53; N, 5.84. M.S. (+ FAB); 694, (Cl=35, 37), (M^+ + 1); 692 (Cl=35, 35), (M^+ + 1).
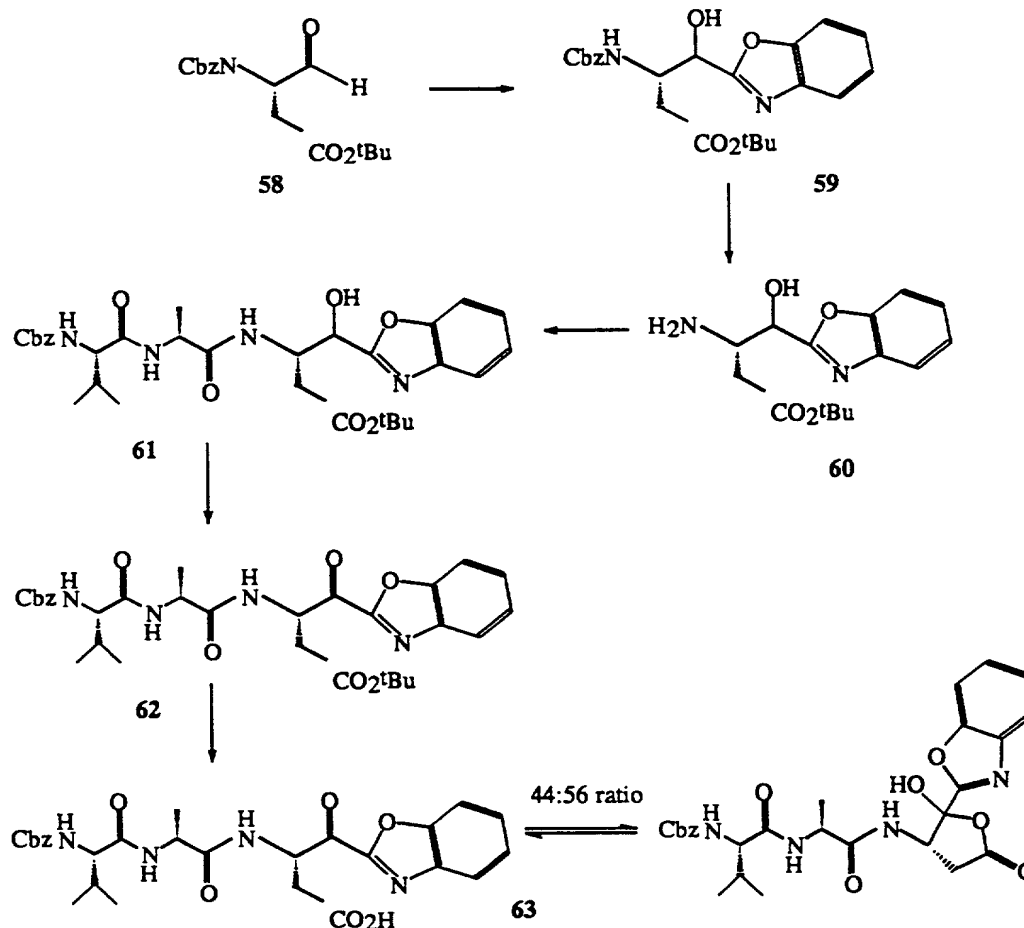
(3S, 4R,S) t-Butyl N-(benzyloxycarbonyl)-3-amino-4-(2-benzoxazolyl)-4-hydroxy-butanoate (59). To a stirred solution of benzoxazole (250.2mg, 2.1mmol) in anhydrous THF (10.5ml) at -78°C under N_2 was added 2.3M n-butyl lithium in hexanes (0.96ml, 2.2mmol) dropwise. After stirring at -78°C for 20min, dry $MgBr_2OEt_2$ (594.0mg, 2.3mmol) was added as a solid. The resulting heterogeneous mixture was warmed to -45°C and stirred for 15min. The reaction mixture was then recooled to -78°C and a solution of aldehyde **58** (Graybill et al., Int. J. Peptide Protein Res., 44, pp. 173-182 (1993)) (644.6mg, 2.1mmol) in THF (10.5ml) was added dropwise.

The reaction was stirred at -78°C for 30min, warmed to 0°C for 1h, and then stirred at room temperature for 16h. The reaction was quenched with 5% sodium bicarbonate (2.0ml) and the THF was removed *in vacuo*. The resulting aqueous residue was extracted four times with methylene chloride. The combined extracts were washed with brine, dried (MgSO$_4$), filtered and reduced *in vacuo* to give 880.0mg of crude product. Flash chromatography (45:55 ethyl acetate/hexane) afforded 567.2mg (63%) of the title compound, an oil, as a mixture of diastereoisomers at C-4. IR (film) 3324, 2976, 1726, 1517, 1455, 1368, 1243, 1159, 1048, 747; ^{1}H NMR (CDCl$_3$) δ 7.71-7.64 (1H, m), 7.52-7.48 (1H, m), 7.37-7.20 (7H, m), 5.91 (1H, brd, J = 9.0), 5.79 (1H, d, J = 9.0), 5.41-4.78 (4H, m), 4.75-4.54 (1H, m), 2.91-2.51 (2H, m), 1.42 (9H, s), 1.37 (9H, s).

(3S, 4R,S) t-Butyl 3-amino-4-(2-benzoxazolyl)-4-hydroxybutanoate (60). A solution of the ester **59** (189.0mg, 0.44mmol) in ethanol (5.0ml) was treated with 10% Palladium on carbon (20.5mg) and stirred under an atmosphere of H$_2$ for 21h. The mixture was filtered through Celite®, and the solvent was evaporated to afford 125.0mg (98%) of crude amine **60** as an oil. This was used without further purification. ^{1}H NMR (CDCl$_3$) δ 7.73-7.64 (1H, m), 7.51-7.42 (1H, m), 7.35-7.22 (2H, m), 6.48 (3H, brs), 5.58 (1H, d, J = 3.0), 5.27 (1H, d, J = 6.5), 4.23-4.05 (1H, m), 2.92-2.63 (2H, m), 1.36 (9H, s), 1.33 (9H, s).

(3S, 4R,S) t-Butyl N-(N-benzyloxycarbonyl-(S)-valinyl-(S)-alaninyl)-3-amino-4-(2-benzoxazolyl)-4-hydroxybutanoate (61). A solution of the amine **60** (261.4mg, 0.89mmol), Z-Val-Ala-OH (286.9mg, 0.89mmol) (prepared by standard peptide synthetic procedures) and

hydroxybenzotriazole (120.3mg, 0.89mmol) in DMF (3.0ml) at 0°C was treated with 1-ethyl-3-[3-(dimethylamino) propyl]carbodiimide hydrochloride (179.2mg, 0.93mmol). The reaction was warmed to room temperature and stirred for 16h. The reaction was diluted with ethyl acetate and washed twice with 1M sodium hydrogensulphate, twice with saturated sodium bicarbonate, then water, and brine. The organic layer was dried ($MgSO_4$), filtered and reduced *in vacuo* to afford 494.8mg of crude product. Flash chromatography (95:5 methylene chloride/methanol) gave 480.9mg (91%) of the title compound as a yellow solid: mp. 81-83°C; IR (KBr) 3312, 2974, 1723, 1709, 1529, 1455, 1368, 1243, 1156, 747; ^1H NMR ($CDCl_3$) δ 7.79 (0.5H, d, J = 8.0), 7.73-7.20 (9.5H, m), 6.15 (1H, t, J = 8.5), 5.74 (0.5H, brd, J = 5.5), 5.45 (1H, brd, J = 7.5), 5.28-5.20 (0.5H, m), 4.82-4.11 (3.5H, m), 4.78-4.55 (1H, m), 4.40-4.22 (1H, m), 2.95-2.51 (2H, m), 2.12-1.95 (1H, m), 1.45-1.32 (12H, m), 1.11-0.81 (6H, m), ^{13}C NMR ($CDCl_3$) δ 173.14, 172.94, 171.82, 171.03, 170.78, 165.98, 165.45, 157.29, 157.17, 151.23, 151.10, 140.92, 140.82, 136.83, 136.79, 128.91, 128.52, 125.75, 124.97, 120.60, 120.40, 111.38, 81.82, 81.68, 70.27, 68.97, 67.44, 60.43, 50.74, 50.55, 49.18, 49.07, 36.87, 36.57, 32.37, 28.51, 19.88, 19.80, 18.53. Anal. Calcd. for $C_{31}H_{40}N_4O_8$. H_2O: C, 60.57; H, 6.89; N, 9.11. Found: C, 60.84; H, 6.64; N, 9.09. M.S. (+ FAB); 597 (M^+ + 1); 541, 91.

(3S) t-Butyl N-(N-benzyloxycarbonyl-(S)-valinyl-(S)-alaninyl)-3-amino-4-(2-benzoxazolyl)-4-oxobutanoate (62). The alcohol **61** (100.3mg, 0.17mmol) was dissolved in methylene chloride (2.0ml) and Dess-Martin reagent (142.6mg, 0.34mmol) was added (Ireland et al., <u>J. Org. Chem.</u>, 58, p. 2899 (1993); Dess et al., <u>J. Org. Chem.</u>, 48, pp. 4155-4156 (1983)). The resulting mixture was

stirred for 22min and then partitioned between saturated sodium thiosulphate: saturated sodium bicarbonate (1:1, 10ml), and ethyl acetate (10ml). The resulting organic phase was washed with saturated sodium thiosulphate, saturated sodium bicarbonate (1:1), saturated sodium bicarbonate, and brine. The organic phase was dried (MgSO$_4$), filtered and reduced *in vacuo* to give 111.3mg of crude product. Flash chromatography (95:5 methylene chloride/methanol) afforded 97.3mg (96%) of the title compound as an oil: $[\alpha]_D^{23}$ -11.74° (c 0.95, CH$_2$Cl$_2$); IR (CH$_2$Cl$_2$) 3419, 2974, 1721, 1677, 1501, 1369, 1221, 1156; ^{1}H NMR (CDCl$_3$) δ 7.89-7.84 (1H, m), 7.73-7.22 (10H, m), 5.98 (1H, d, J = 9.0), 5.72 (1H, m), 5.10 (2H, q, J = 12.5), 4.73 (2H, m), 4.20 (1H, dd, J = 7.0, 8.5), 3.30 (1H, dd, J = 5.0, 16.5), 3.03 (1H, dd, J = 5.5, 16.5), 2.18-1.97 (1H, m), 1.39 (3H, d, J = 7.0), 1.34 (9H, s), 0.93 (3H, d, J = 6.0), 0.90 (3H, d, J = 6.0), ^{13}C NMR (CDCl$_3$) δ 186.46, 172.73, 171.90, 170.13, 157.17, 156.28, 151.16, 140.99, 136.99, 129.39, 129.08, 128.66, 128.59, 126.49, 123.06, 112.55, 82.73, 67.60, 60.84, 53.75, 49.41, 38.58, 32.05, 28.52, 19.85, 19.32, 18.51. M.S. (+ FAB); 595 (M$^+$ + 1); 539, 91.

(3S) N-(N-Benzyloxycarbonyl-(S)-valinyl-(S)-alaninyl)-3-amino-4-(2-benzoxazolyl)-4-oxobutanoate (63; Q). A solution of the ester 62 (95.0mg, 0.16mmol) in a 1:1 mixture of methylene chloride and trifluoroacetic acid (10.0ml) was stirred for 1h under a dry atmosphere of N$_2$. The solution was then reduced *in vacuo*, taken up in ether and reduced again. This process was repeated six times to afford the crude product as an off white solid. Flash chromatography (95:5 methylene chloride/methanol) gave 60.0mg (69%) of the title compound as a white solid. The product existed as a

mixture of three isomers in CD_3OD, consisting of the
ketone form (one isomer, c 44%), and its acycloxy ketal
form (two isomers at C-4, c. 56%): m.p. 156-159°C $[\alpha]_D^{26}$
-45.6° (c 0.13, methanol); IR (KBr) 3440, 2967, 1713,
1703, 1638, 1531, 1427; ^1H NMR (CD_3OD) δ 7.93-7.24 (9H,
m), 5.59 (1H, brt), 5.16-5.00 (2H, m), 5.0-4.78 (1H,
m), 4.50-4.22 (1H, m), 3.95-3.81 (1H, m), 3.11 (2H, d,
J = 6.5), 3.05-2.92 (1H, m), 2.70-2.39 (1H, m), 2.08-
1.89 (1H, m), 1.19-0.78 (9H, m). Anal. Calcd. for
$C_{27}H_{30}N_4O_8$. $0.5H_2O$: C, 59.22; H, 5.71; N, 10.23. Found:
C, 59.48, H, 5.36, N, 10.17. M.S. (+ FAB); 539 (M^+ +
1), 91.
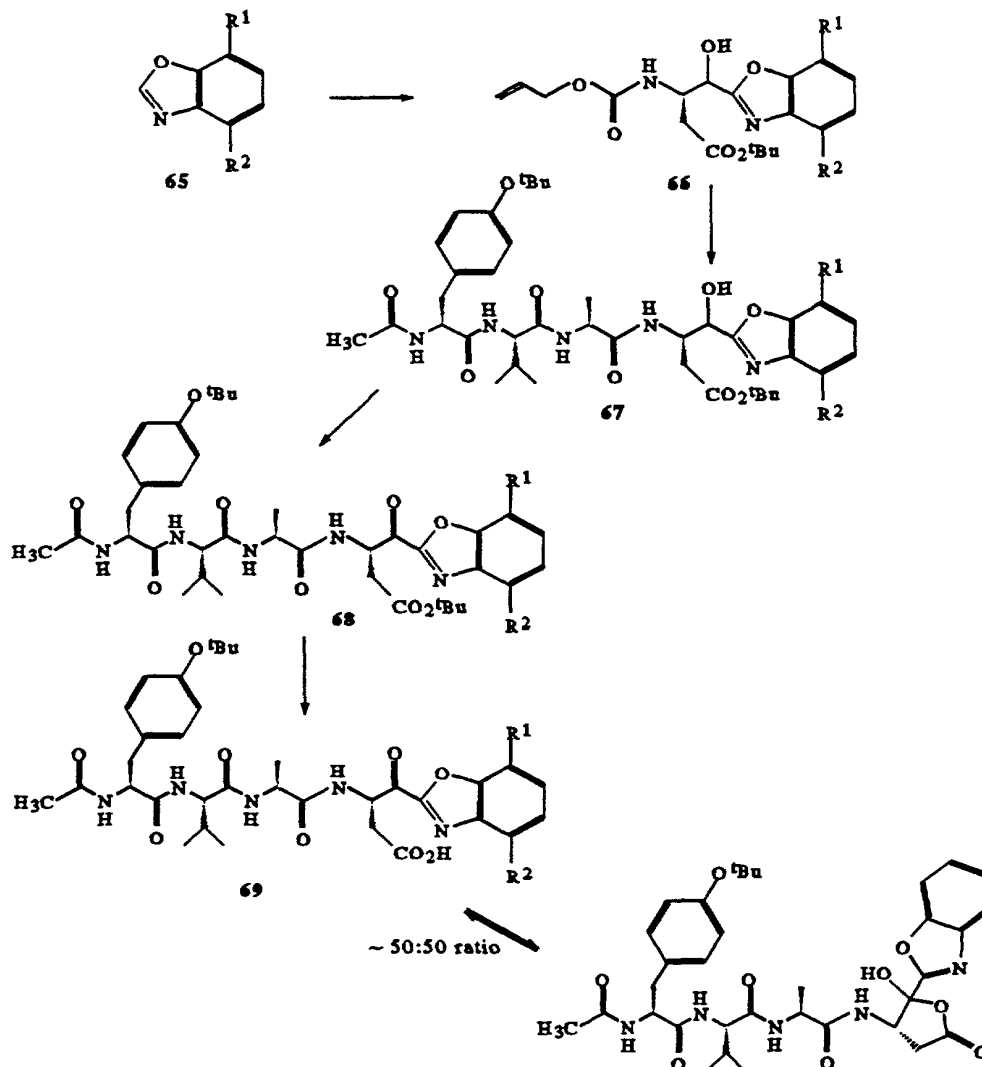
(a) R^1 = OCH_3, R^2 = H

(b) R^1 = H, R^2 = OCH_3

7-Methoxybenzoxazole (65a). A mixture of 2-nitro-6-methoxyphenol (2.62g, 15.5mmol) (EP 333176) and 10%

5 Palladium on carbon (130mg) in ethanol (50.0ml) was stirred under an atmosphere of H_2 for 75min. The mixture was filtered through Celite® then immediately treated with p-toluenesulphonic acid (32.0mg) and triethylorthoformate (6.45ml, 38.8mmol) then heated

10 under reflux under an atmosphere of N_2. After 20h p-

toluenesulphonic acid (30.0mg) and triethylorthoformate (6.45ml, 38.8mmol) were added. After a total of 44h heating, the reaction was allowed to cool and reduced *in vacuo*. The resulting residue was purified by flash chromatography (25:75 ethyl acetate/hexane) to give 1.97g (85%) of the title compound as a yellow solid: m.p. 28-31°C; IR (film) 1629, 1497, 1434, 1285, 1097; ^{1}H NMR (CDCl$_3$) δ 8.09 (1H, s), 7.40 (1H, d, J = 8.0), 7.28 (1H, t, J = 8.0), 6.89 (1H, d, J = 8.0), 4.02 (3H, s); ^{13}C NMR (CDCl$_3$) δ 152.84, 145.82, 142.50, 139.99, 125.75, 113.42, 108.80, 56.97. Anal. Calcd. for C$_8$H$_7$N$_1$O$_2$. 0.1H$_2$O: C, 63.65; H, 4.81; N, 9.29. Found: C, 63.43, H, 4.88, N, 9.05. M.S. (+ FAB); 150 (M$^+$ + 1).

4-Methoxybenzoxazole (65b). To a suspension of 4-hydroxybenzoxazole (2.00g, 14.8mmol) (Musser et al., _J. Med. Chem._, 30, pp. 62-67 (1987)) in acetone (80.0ml) was added dried K$_2$CO$_3$ (2.25g, 16.3mmol) followed by iodomethane (1.38ml, 22.2mmol). The reaction was heated under reflux under N$_2$ for 4.5h, then filtered and reduced *in vacuo* to afford the crude product. The resulting residue was purified by flash chromatography (25:75 ethyl acetate/hexane) to give 2.0g (91%) of the title compound as a white crystalline solid: m.p. 72-74°C; IR (KBr) 3089, 1619, 1610, 1503, 1496, 1322, 1275, 1090, 1071, 780, 741; ^{1}H NMR (CDCl$_3$) δ 8.02 (1H, s), 7.32 (1H, t, J = 8.0), 7.18 (1H, d, J= 8.0), 6.81 (1H, d, J = 8.0), 4.04 (3H, s). Anal. Calcd. for C$_8$H$_7$NO$_2$: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.40; H, 4.84; N, 9.31; m/z (EI) 149 (M$^+$ + 1, 100%).

(3*S*, 4*R*,*S*) t-Butyl N-(allyloxycarbonyl)-3-amino-4-hydroxy-4-(2-(7-methoxybenzoxazolyl))butanoate (66a). To a stirred solution of 7-methoxybenzoxazole 65a (548.6mg, 3.68mmol) in anhydrous THF (18.5ml) at -78°C

under N_2 was added 1.56M *n*-butyl lithium in hexanes
(2.47ml, 3.86mmol) dropwise, to produce a yellow
colored solution. After stirring at -78°C for 20 min,
dry $MgBr_2OEt_2$ (1.045g, 4.05mmol) was added as a solid.
The resulting heterogeneous mixture was warmed to -45°C
and stirred for 15min. The reaction mixture was then
recooled to -78°C and a solution of (S)-Alloc-Asp(*t*-
Bu)H[1b] (946.4mg, 3.68mmol) in THF (18.5ml) was added
dropwise. The reaction was stirred at -78°C for 30min,
warmed to 0°C and stirred for 1h. The resulting
homogeneous reaction was warmed to room temperature and
stirred for 16h. The reaction was quenched with 5%
sodium bicarbonate (3.5ml) then THF was removed *in
vacuo*. The resulting aqueous residue was extracted
with methylene chloride (x6). The combined extracts
were washed with brine, dried ($MgSO_4$), filtered and
reduced *in vacuo* to give 1.8g of crude product. Flash
chromatography (40:60 ethyl acetate/hexane) gave 1.21g
(81%) of the title compound, an oil, as a mixture of
diastereoisomers at C-4: IR (CH_2Cl_2) 3425, 2983, 1725,
1504, 1290, 1157, 1101; ^{1}H NMR ($CDCl_3$) δ 7.35-7.19 (2H,
m), 6.89-6.81 (1H, m), 6.00-5.57 (2H, m), 5.32-5.05
(3H, m), 4.68-4.35 (3H, m), 4.01 (3H, s), 2.86-2.59
(2H, m), 1.45 (9H, s), 1.41 (9H, s); ^{13}C NMR ($CDCl_3$) δ
171.18, 171.09, 165.80, 165.30, 156.71, 156.60, 145.65,
142.76, 142.71, 140.82, 140.72, 133.23, 125.81, 125.72,
118.41, 118.21, 113.07, 112.87, 108.95, 82.16, 70.28,
69.98, 66.52, 66.39, 57.03, 52.57, 52.29, 37.83, 36.86,
28.65. Anal. Calcd. for $C_{20}H_{26}N_2O_7$. 0.6H_2O: C, 57.57; H,
6.57; N, 6.72. Found: C, 57.49, H, 6.34, N, 6.60. M.S.
(+ FAB); 407 (M^+ + 1); 351, 307, 154.

(3*S*, 4*R,S*) t-Butyl N-(allyloxycarbonyl)-3-amino-4-
hydroxy-4-(2-(4-methoxybenzoxazolyl))butanoate (66b),
was prepared according to the method described for 66a

which afforded 1.29g (26%, 68% based on recovered starting material) of the title compound as an oil and as a mixture of diastereoisomers at C-4:   IR (CH_2Cl_2) 3400, 1725, 1625, 1505, 1369, 1354, 1281, 1263, 1226, 1158, 1092, 1048; ^1H NMR ($CDCl_3$) δ 7.34-7.24 (1H, m), 7.16 (1H, d, J = 8.2), 6.79 (1H, d, J = 7.9), 6.00-5.50 (2H, m), 5.30-5.05 (3H, m), 4.70-4.35 (4H, m), 4.02 (3H, s), 2.90-2.45 (2H, m), 1.45-1.41 (9H, 2 x s). Anal. Calcd. for $C_{20}H_{26}N_2O_7$. $0.4H_2O$: C, 58.07; H, 6.53; N, 6.77. Found: C, 58.09; H, 6.41; N, 6.63. M.S. (+ FAB); 407 (M^+ + 1, 88%); 351 (100).

(3*S*, 4*R*,*S*) t-Butyl N-(N-acetyl-(S)-(O-tert-butyl-tyrosinyl)-(S)-valinyl-(S)-alaninyl)-3-amino-4-hydroxy-4-(2-(7-methoxybenzoxazolyl))butanoate (67a). To a stirred solution of the benzoxazole **66a** (481.9mg, 1.19mmol) and Ac-Tyr(^tBu)-Val-Ala-OH (586.3mg, 1.30mmol) in methylene chloride (3.5ml) and DMF (3.5ml) was added bis(triphenylphosphine) palladium (II) chloride (18.0mg), followed by tributyltinhydride (0.80ml, 2.96mmol) dropwise. Hydroxybenzotriazole (320.4mg, 2.37mmol) was added and the mixture cooled to 0°C.   1-Ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (278.2mg, 1.42mmol) was added and the mixture was allowed to warm to room temperature and stirred for 16.5h. The reaction was diluted with ethyl acetate and washed twice with 1M sodium hydrogensulphate, twice with saturated sodium bicarbonate, water, and brine. The organic layer was dried ($MgSO_4$), filtered and reduced *in vacuo* to yield 2.0g of crude product. Flash chromatography (95:5 methylene chloride/methanol) gave 844.0mg (94%) of the title compound as a white solid: m.p. 205°C; IR (KBr) 3399, 3304, 2977, 1729, 1643, 1506, 1367, 1290, 1161; ^1H NMR (d_6-DMSO) δ 8.24-7.78 (4H, m), 7.43-7.32 (2H, m),

7.23 (2H, d, J = 8.5), 7.16-7.07 (1H, m), 6.93 (2H, d, J = 8.5), 6.52, 6.40 (1H, 2 x d, J = 5.5, J= 5.0), 5.03, 4.78-4.49, 4.45-4.16 (5H, brt, 2 x m), 4.05, 4.04 (3H, 2 x s), 3.08-2.35 (14H, m), 2.11-1.89 (1H, m), 1.83 (3H, s), 1.49-1.32, 1.15, 1.0-0.81 (27H, s, 2 x m, J = 7.0); ^{13}C NMR (d_6-DMSO) δ 175.55, 175.18, 173.88, 173.75, 173.05, 169.23, 157.28, 148.55, 146.16, 143.21, 136.63, 133.55, 128.87, 127.17, 115.78, 111.92, 84.02, 81.50, 71.40, 61.15, 60.05, 57.79, 53.39, 51.62, 43.76, 40.52, 34.58, 32.52, 31.60, 26.35, 23.11, 22.71, 21.76. Anal. Calcd. for $C_{39}H_{55}N_5O_{10}$. 0.5H_2O: C, 61.40; H, 7.40; N, 9.18. Found: C, 61.43; H, 7.31; N, 9.07. M.S. (+ FAB); 754 (M^+ + 1); 698, 338, 267.

(3S, 4R,S) t-Butyl N-(N-acetyl-(S)-(O-tert-butyl-tyrosinyl)-(S)-valinyl-(S)-alaninyl)-3-amino-4-hydroxy-4-(2-(4-methoxybenzoxazolyl))butanoate (67b), was prepared according to the method described for **67a** which afforded 1.05g (94%) of the title compound as a fine white powder: m.p. 210-213°C (dec); IR (KBr) 3284, 2977, 1736, 1691, 1632, 1536, 1505, 1452, 1392, 1367, 1258, 1236, 1161, 1091; ^{1}H NMR (d_6-DMSO) δ 8.20-7.75 (4H, m), 7.40-7.10 (4H, m), 7.00-6.80 (3H, m), 6.45, 6.34 (1H, 2 x d, J = 5.3, J = 5.0), 5.00-4.10 (5H, m), 4.00, 3.99 (3H, 2 x s), 3.00-2.25 (4H, m), 1.95 (1H, m), 1.78 (3H, s), 1.39-0.80 (27H, m). Anal. Calcd. for $C_{39}H_{55}N_5O_{10}$. 0.5H_2O: C, 61.40; H, 7.40; N, 9.18. Found: C, 61.58; H, 7.38; N, 8.91. M.S. (+ FAB); 754 (M^+ + 1, 30%); 72 (100).

(3S) t-Butyl N-(N-acetyl-(S)-(O-tert-butyl-tyrosinyl)-(S)-valinyl-(S)-alaninyl)-3-amino-4-(2-(7-methoxybenzoxazolyl))-4-oxobutanoate (68a). The Dess-Martin reagent (1.082g, 2.55mmol) (Ireland et al., <u>J. Org. Chem.</u>, 58, p. 2899 (1993); Dess et al., <u>J. Org.</u>

<u>Chem.</u>, 48, pp. 4155-4156 (1983)) was added to a stirred suspension of the alcohol **67a** (641.0mg, 0.85mmol) in methylene chloride (46.0ml). The resulting mixture was stirred for 1h before being partitioned between saturated sodium thiosulphate: saturated sodium bicarbonate (1:1, 86.0ml) and ethyl acetate (86.0ml). The resultant organic phase was washed in turn with saturated sodium thiosulphate: saturated sodium bicarbonate (1:1), saturated sodium bicarbonate, and brine. The organic phase was dried (MgSO$_4$), filtered and reduced *in vacuo* to give 660.0mg of crude product. Flash chromatography (94:6 methylene chloride/methanol) gave 636.0mg (100%) of the title compound as a white solid: m.p. 209°C; $[\alpha]_D^{24}$ -21.8° (c 0.16, methanol); IR (KBr) 3395, 3294, 2977, 1722, 1641, 1535, 1505, 1161; ^{1}H NMR (CDCl$_3$) δ 8.43-8.16 (1H, m), 7.97-7.62 (2H, m), 7.49-7.14 (3H, m), 7.08-6.95 (3H, m), 6.89-6.73 (2H, m), 5.81-5.68 (1H, m), 5.16-4.86 (2H, m), 4.53 (1H, brt), 4.03 (3H, s), 3.16-2.84 (4H, m), 2.11-1.84 (4H, m), 1.46-1.14 (21H, m), 0.92-0.78 (6H, m); ^{13}C NMR (CDCl$_3$) δ 186.28, 173.39, 171.90, 171.19, 171.03, 169.89, 156.43, 154.75, 146.32, 142.88, 140.98, 132.31, 130.54, 126.98, 124.73, 114.95, 111.42, 82.44, 78.71, 58.92, 57.20, 54.91, 53.47, 48.77, 39.43, 38.15, 32.79, 29.44, 28.60, 23.55, 20.27, 19.70, 19.34. M.S. (+ FAB); 752 (M$^+$ + 1); 696, 336, 265.

(3S) t-Butyl N-(N-acetyl-(S)-(O)-tert-butyl-tyrosinyl)-(S)-valinyl-(S)-alaninyl)-3-amino-4-(2-(4-methoxybenzoxazolyl))-4-oxobutanoate (68b), was prepared according to the method described for the ketone **68a** which afforded 420mg (55%) of the title compound as a white solid: m.p. 211-213°C (dec); $[\alpha]_D^{24}$ -23.9° (c 0.82, methanol); IR (KBr) 3277, 3075, 1723, 1690, 1632, 1530, 1506, 1392, 1366, 1269, 1234, 1160,

1094; ^{1}H NMR (CDCl$_3$) δ 8.15 (1H, brs), 7.7 (2H, brs), 7.46 (1H, t, J = 8.3), 7.24 (2H, d, J = 8.3), 7.10 (1H, brs), 7.03 (2H, d, J = 8.3), 6.83 (3H, m), 5.74 (1H, q, J = 6.9), 5.00 (2H, m), 4.51 (1H, t, J = 7.0), 4.07 (3H, s), 3.20-2.95 (4H, m), 2.00 (4H, m), 1.42 (3H, d, J = 6.8), 1.35 (9H, s), 1.23 (9H, s), 0.86 (6H, d, J = 6.7). M.S. (+ FAB); 752 (M$^+$ + 1, 7%); 72 (100).

(3S) N-(N-Acetyl-(S)-tyrosinyl-(S)-valinyl-(S)-alaninyl)-3-amino-4-(2-(7-methoxybenzoxazolyl))-4-oxobutanoate (69a; R). A solution of the ester **68a** (600.0mg, 0.80mmol) in a 1:1 mixture of methylene chloride and trifluoroacetic acid (65.0ml) was stirred for 1h under a dry atmosphere of N$_2$. The solution was then reduced *in vacuo*, taken up in ether and reduced again. This process was repeated six times to afford the crude product as an off white solid. Flash chromatography (gradient 95:5 to 80:20 methylene chloride/methanol) gave 420.8mg (83%) of the title compound as a hygroscopic white solid. The product existed as a mixture of three isomers in CD$_3$OD, consisting of the keto form (c 50%), and its acycloxy keto form (two isomers at C-4, c 50%): m.p. decomposes above 150°C; [α]$_D^{24}$-33.2° (c 0.17, methanol); IR (KBr) 3300, 1715, 1658, 1650, 1531, 1517, 1204; ^{1}H NMR (CD$_3$OD) δ 7.46-7.19 (2H, m), 7.16-6.91 (3H, m), 6.70-6.59 (2H, m), 5.62-5.49 (1H, m), 5.00-4.72 (1H, obscurred m), 4.69-4.51 (1H, m), 4.49-4.08 (2H, m), 4.05-3.89 (3H, m), 3.16-2.47 (4H, m), 2.05-1.78 (4H, m), 1.41-1.11, 1.05-0.70 (9H, 2 x m). Anal. Calcd. for C$_{31}$H$_{37}$N$_5$O$_{10}$·3H$_2$O: C, 53.67; H, 6.25; N, 10.10. Found: C, 53.76; H, 5.56; N, 10.28. M.S. (+ FAB); 640 (M$^+$ + 1); 435, 147.

(3S) t-Butyl N-(N-acetyl-(S)-tyrosinyl-(S)-valinyl-(S)-alaninyl)-3-amino-4-(2-(4-methoxybenzoxazolyl))-4-oxobutanoate (69b; $\underline{S}$), was prepared according to the method described for the acid **69a** which afforded the hygroscopic title compound 252mg (96%). The product existed as a mixture of three isomers in CD_3OD, consisting of the keto form, and its acycloxy ketal form (two isomers at C-4). The product existed as a single isomer in d-6 DMSO: m.p. 200-203°C (dec.); $[\alpha]_D^{24}$ -38.0° (c 0.23, methanol); IR (KBr) 3289, 2968, 1718, 1713, 1658, 1634, 1548, 1517, 1506, 1461, 1453, 1393, 1369, 1268, 1228, 1174, 1092; ^{1}H NMR (d_6-DMSO) δ 9.20 (1H, brs), 8.71 (1H, d, J = 6.2), 8.10 (2H, m), 7.83 (1H, d, J = 8.7), 7.61 (1H, t, J = 8.2), 7.46 (1H, d, J = 8.2), 7.08 (3H, m), 6.65 (2H, d, J = 8.3), 5.50 (1H, q, J = 6.5), 4.50 (1H, m), 4.37 (1H, m), 4.20 (1H, m), 4.05 (3H, s), 3.09-2.77 (4H, m), 1.94 (1H, m), 1.79 (3H, s), 1.23 (3H, d, J = 7.0), 0.82 (6H, m). Anal. Calcd. for $C_{31}H_{37}N_5O_{10}$. $1.5H_2O$: C, 55.85; H, 6.05; N, 10.51. Found: C, 55.21; H, 5.69; N, 10.13. M.S. (+ FAB); 640 (M^+ + 1, 22%); 107 (100).
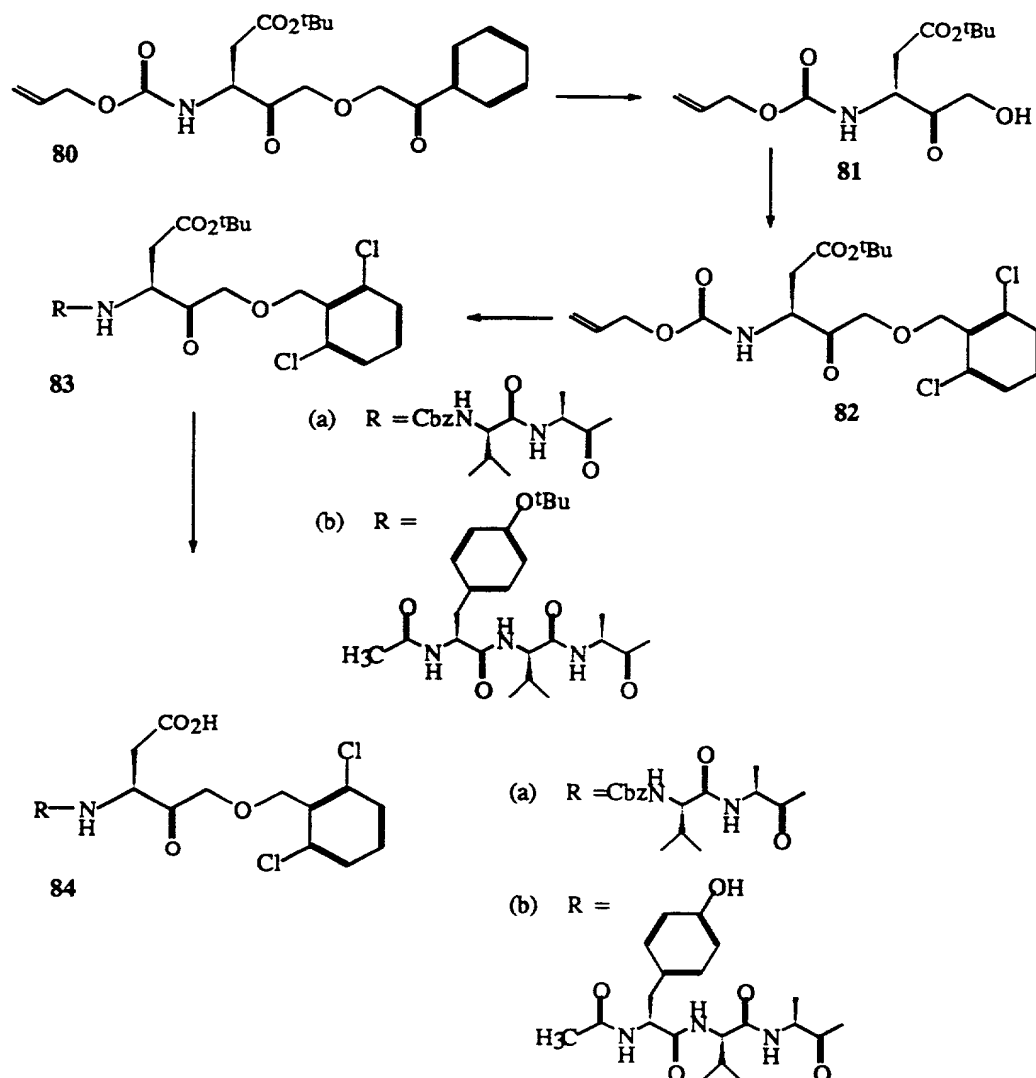
3S) t-Butyl N-(allyloxycarbonyl)-3-amino-4-oxo-5-(1,2-dioxo-2-phenylethyloxy)-pentanoate (80). Potassium fluoride (792mg, 13.6mmol) and then benzoyl formic acid (1.02g, 6.82mmol) were added to a stirred solution of (3S) t-butyl N-(allyloxycarbonyl)-3-amino-5-bromo-4-oxo-pentanoate (WO 93 16710) (2.17g, 6.20mmol) in dimethylformamide (30ml). The mixture was stirred for 140 mins, quenched with water (50ml) and extracted with

ethyl acetate (2 x 50ml). The combined organic extracts were washed with water (4 x 50ml) then brine (50ml). They were dried (MgSO$_4$) and concentrated to afford an oil which was purified by flash chromatography (20-45% ethyl acetate in hexane) to afford 2.44g (94%) of a colorless oil: $[\alpha]_D^{20}$ -35.0° (c 1.41, CH$_2$Cl$_2$); IR (film) 3359, 2981, 2938, 1752, 1740, 1726, 1712, 1512, 1369, 1285, 1177, 1053, 991, 939, 688; ^{1}H NMR (CDCl$_3$) δ 8.15 (2H, m), 7.66 (1H, m), 7.53 (2H, m), 5.90 (2H, m), 5.33 (2H, m), 5.31 (1H, d, J = 16.9), 5.18 (1H, d, J = 16.9), 4.63 (3H, m), 3.03 (1H, dd, J = 17.3, 4.6), 2.74 (1H, dd, J = 17.3, 4.9), 1.44 (9H, s). MS (C.I.) 420 (M$^+$ + 1 20%); 364 (100).

(3S) t-Butyl N-(allyloxycarbonyl)-3-amino-5-hydroxy-4-oxo-pentanoate (81). A mixture of the ester **80** (2.40g, 5.71mmol), tetrahydrofuran (200ml) and 1M aqueous potassium bicarbonate (200ml) was vigorously stirred at room temperature for 18h. The layers were separated and the aqueous portion extracted with ethyl acetate (100ml). The combined organic extracts were washed with brine (100ml), dried (MgSO$_4$) and concentrated. The residue was purified by flash chromatography (10-60% ethyl acetate in hexane) to afford 1.48g (90%) of pale yellow oil: $[\alpha]_D^{20}$ -5.9° (c 1.06, CH$_2$Cl$_2$); IR (film) 3345, 2981, 2936, 1739, 1725, 1712, 1692, 1515, 1368, 1259, 1158, 1051; ^{1}H NMR (CDCl$_3$) δ 5.92 (2H, m), 5.30 (2H, m), 4.36-4.69 (5H, m), 3.05 (1H, dd, J = 17.4, 4.3), 2.93 (1H, t), 2.70 (1H, dd, J = 17.4, 4.9), 1.43 (9H, s). Anal. Calcd for C$_{18}$H$_{21}$N$_1$O$_6$. 0.25H$_2$O: C, 53.51; H, 7.43; N, 4.80. Found: C, 53.61; H, 7.18; N, 4.71. MS (C.I.) 280 (M$^+$ + 1, 87%); 232 (100).

(3*S*) t-Butyl N-(allyloxycarbonyl)-3-amino-5-(2,6-dichlorophenyl-methoxy)-4-oxo-pentanoate (82). A stirred mixture of alcohol 81 (1.44g, 5.01mmol), 2,6-dichlorobenzyl iodide (Abraham et al., J. Chem. Soc., pp. 1605-1607 (1936)) (4.31g, 15.0mmol), silver oxide (2.32g, 10.0mmol) and dichloromethane (25ml) was heated under reflux for 45h. The mixture was allowed to cool to room temperature then diluted with water (50ml) then extracted with ethyl acetate (50ml, 25ml). The organic layer was washed with water (50ml) then brine (50ml), dried (MgSO$_4$), and concentrated. The residue was purifed by flash chromatography (10-100% ethyl acetate in hexane) to afford 1.65g (74%) of a colorless oil: [α]$_D^{20}$ +8.8° (c 1.13, CH$_2$Cl$_2$); IR (film) 3339, 2980, 2935, 1724, 1712, 1503, 1438, 1368, 1246, 1156, 1106, 770; ^{1}H NMR (CDCl$_3$) δ 7.33 (2H, m), 7.22 (1H, dd), 5.92 (2H, m), 5.28 (2H, m), 4.87 (2H, m), 4.67 (1H, m), 4.58 (2H, br d), 4.56 (1H, d, *J* = 16.9), 4.31 (1H, d, *J* = 16.9), 3.04 (1H, dd, *J* = 16.7, 4.5), 2.77 (1H, dd, *J* = 16.7, 4.9), 1.40 (9H, s). Anal. Calcd. for C$_{20}$H$_{25}$Cl$_2$N$_1$O$_6$. 0.25H$_2$O: C, 53.28; H, 5.70; N, 3.11. Found: C, 53.15; H, 5.52; N, 2.98. M.S. (C.I.); 446 (M$^+$, 27%); 390 (100).

(3*R,S*) t-Butyl N-[N-phenylmethyloxycarbonylvalaninyl-alaninyl]-3-amino-5-(2,6-dichlorophenylmethyloxy)-4-oxo-pentanoate (83a). 1-(3-Dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride (379g, 1.98mmol) and 1-hydroxybenzotriazole (486mg, 3.60mmol) were added to a stirred solution of N-phenyl-methyloxycarbonylvalinyl-alanine (637mg, 1.98mmol) in tetrahydrofuran (40ml) and water (1ml). The mixture was stirred for 15mins and then the ether 82 (802mg, 1.80mmol) and bis(triphenyl-phosphine)palladium (II) chloride (ca 5mg) were added.

Tributyltin hydride (785mg, 725 l, 2.70mmol) was then
added dropwise during 20mins and the resulting solution
was stirred for 3.75h and then quenched with 1M
hydrochloric acid (50ml). The mixture was extracted
twice with ethyl acetate. The combined organic
extracts were washed with 1M hydrochloric acid, twice
with aqueous sodium bicarbonate, water and then brine,
dried (MgSO$_4$) and concentrated. The residue was
purified by flash chromatography (10-30% ethyl acetate
- dichloromethane) to afford 941mg (79%) of pale yellow
solid: m.p. 148-52°C; IR (KBr) 3287, 3070, 1730, 1691,
1641, 1536, 1369, 1289, 1247, 1156; ^{1}H NMR (CDCl$_3$) δ
7.33 (8H, m), 7.23 (1H, dd), 6.61 (1H, br, d), 5.42
(1H, br, d), 5.11 (2H, s), 4.85 (3H, m), 4.50 (1H, m),
4.40 (1H, d, J = 16.9), 4.26 (1H, d, J = 16.9), 4.02
(1H, m), 2.99 (1H, dd, J = 16.8, 4.7), 2.73 (1H, dd, J
= 16.8, 5.0), 2.09 (1H, m), 1.37 (12H, m), 0.96 (3H, d,
J = 6.9), 0.91 (3H, d, J = 6.8). Anal. Calcd. for
C$_{32}$H$_{41}$Cl$_2$N$_3$O$_8$. 0.25H$_2$O: C, 57.25; H, 6.23; Cl, 10.57; N,
6.26. Found: C, 57.18; H, 6.23; Cl, 10.58; N, 5.95.
M.S. (+ FAB); 667 (M$^+$ 1, 1%); 666 (3), 159 (25), 91
(100).

**(3R,S) t-Butyl N-[(N-acetyl-O-t-butyltyrosinyl)-
valaninyl-alaninyl]-3-amino-5-(2,6-
dichlorophenylmethyloxy)-4-oxo-pentanoate (83b),** was
prepared by the method described for **83a** to afford
554mg (64%) of colorless solid: m.p. 184-6°C; IR (KBr)
3282, 3075, 1736, 1690, 1633, 1536, 1508, 1366, 1236,
1161; ^{1}H NMR (d$_6$-DMSO) δ 8.49 (1H, d), 8.14 (1H, d),
8.08 (1H, d), 7.84 (1H, d), 7.43 (3H, m), 7.14 (2H, d),
6.83 (2H, d), 4.71 (2H, s), 4.51 (2H, m), 4.36 (2H,
dd), 4.17 (2H, m), 2.93 (1H, m), 2.73 (1H, m), 1.94
(1H, m), 1.74 (3H, s), 1.37 (9H, s), 1.23 (12H, m),

0.83 (6H, m). M.S. (+ FAB); 793 (M⁺ 1, 4%); 737 (5),
681 (1), 178 (40), 159 (45), 136 (100), 107 (40). M.S.
(- FAB); 792 (20), 791 (40), 447 (100).

(*R,S*) N-[N-(Phenylmethyloxy)carbonyl-valinyl-alaninyl]-
3-amino-5-(2,6-dichlorophenylmethyloxy)-4-oxo-pentanoic
acid (84a; $\underline{V}$). Trifluoroacetic acid (5ml) was added to
a stirred solution of the ester 83a, (918mg, 1.38mmol)
in dichloromethane (20ml). The mixture was stirred for
2.5h then evaporated to dryness. The residue was
treated with ether (25ml) and evaporated to dryness.
This procedure was repeated three times. The resulting
product was triturated with ether (10ml) and then dried
to afford 730mg (87%) of light brown powder: m.p. 156-
60°C; IR (KBr) 3282, 2965, 1702, 1694, 1642, 1536,
1438, 1246, 1230; ¹H NMR (d₆-DMSO) δ 8.48 (1H, d), 8.09
(1H, d), 7.47 (9H, m), 5.02 (2H, s), 4.70 (2H, s), 4.49
(1H, m), 4.37 (2H, dd), 4.27 (1H, m), 3.88 (1H, m),
2.75 (1H, dd), 2.54 (1H, dd), 1.96 (1H, m), 1.19 (3H,
s), 0.84 (6H, m). Anal. Calcd. for $C_{28}H_{33}Cl_2N_3O_8.$ $0.5H_2O$:
C, 54.27; H, 5.53; Cl, 11.45; N, 6.78. Found: C,
54.49; H, 5.39; Cl, 11.33; N, 6.73. M.S. (+ FAB); 610
(M⁺ 1, 10%); 91 (100).

(*R,S*) N-[N-(Acetyl)tyrosinyl-valinyl-alaninyl]-3-amino-
5-(2,6-dichlorophenylmethyloxy)-4-oxo-pentanoic acid
(84b; $\underline{W}$), was obtained as a colorless powder (95%) by
the method used for 84a. m.p. 165-8°C: IR (KBr) 3295,
2968, 1733, 1642, 1517, 1438, 1231, 1105; ¹H NMR (d₆-
DMSO) 9.2 (1H, br, s), 8.48 (1H, br, d), 8.14 (1H,
br, d), 8.02 (1H, br, d), 7.81 (1H, br, d), 7.45 (3H,
m), 7.02 (2H, d), 6.62 (2H, d), 4.70 (2H, s), 4.12-4.53
(3H, m), 3.60 (3H, m), 2.51-2.92 (4H, m), 1.96 (1H, m),
1.75 (3H, s), 1.21 (3H, d), 0.83 (6H, m). Anal. Calcd.

for $C_{31}H_{38}Cl_2N_4O_9 \cdot H_2O$: C, 53.22; H, 5.76; Cl, 10.14; N, 8.09. Found: C, 53.33; H, 5.54; Cl, 10.02; N, 7.85. M.S. (+ FAB); 682 (M^+ 2, 30%); 681 (67), 158 (100). (- FAB); 680 (45), 679 (100).

Example 6

We obtained inhibition constants (K_i) and IC_{50} values for several compounds of this invention using enzyme assays with UV-visible substrate, fluorescent substrate, and cell assays as described in Example 2. The following K_i and IC_{50} values were determined for compounds 22e, 54b, 54j, 54k, 57b, 85, 86, 87, 88, 89, 90, 91, 92, 98, 102a-c, 106a-c, 108a-c, 114a, 114b, 115, 121, 125a, 125b, 126, 127, 128, 129, 130, 131, 132a, 132b, 133, 135a, 135b, 136, 137, 138, 139, 140, 141, 142, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, and 163 using the indicated assays. The structures of compounds 22e, 54b, 54j, 54k, and 57b are shown in Example 5. The other compound structures are shown in Example 7.

| | Assay | |
Compound	UV-visible K_i (μM)	Cell IC_{50} (μM)
22e	0.19	>20
54b		20
54j		10
54k		6.6
57b		2.2
85	0.0035	9.8

	86	0.175	4.0
	87	7.2	35.0
	88	0.9	
	89	0.018	
5	90	0.42	6.2
	91	0.26	>25
	92	3.8	
	98	0.535	4.0
	102a		4.0
10	102b	0.29	1.75
	102c	0.68	
	106a	2.3	30.0
	106b	0.2	2.9
	106c	3.8	>30.0
15	108a		17.5
	108b	0.4	25.0
	108c	0.43	
	114a	0.12	3.8
	114b	3.7	
20	115	0.345	6.0
	121	4.3	
	125a	0.39	>30.0
	125b	0.060	0.30
	126	0.45	1.5
25	127	0.39	8.0
	128	0.04	7.5
	129	0.59	25.0
	130		1.20
	131	12.0	30.0
30	132a	5.0	>30.0
	132b	12.5	
	133	50.0	>30.0
	135a	0.090	0.90
	135b	0.32	0.95

	136		1.0
	137	0.04	0.25
	138		0.375
	139	0.350	2.0
5	140	0.87	>30.0
	141	0.670	
	142		1.75
	144	0.32	>20.0
	145	0.34	8.5
10	146	0.16	3.8
	147	0.26	8.5
	148	6.3	30.0
	149	14.0	>30.0
	150	10.0	30.0
15	151	13.0	30.0
	152	8.8	
	153	0.24	
	154	0.042	2.4
	155	0.023	
20	156	0.001	2.7
	157	0.26	
	158	1.1	
	159	0.0017	8.0
	160	0.145	2.25
25	161	0.011	
	162	0.0025	
	163	0.0028	1.2

Example 7

30   Compounds 126, 127, 128, 129, 135a, 135b, 137
144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154,
155, 156, 157, 159, 160, 162, and 163 were synthesized

by a method similar to the method used in the synthesis of 69a.

126

127

128

129

135a

135b

137

144

5

145

10

146

147

15

148

149

20

150

;

151

;

152

;

153

;

154

;

155

;

156

;

5

10

157

;

159

;

5

160

;

162

; and

10

163

.
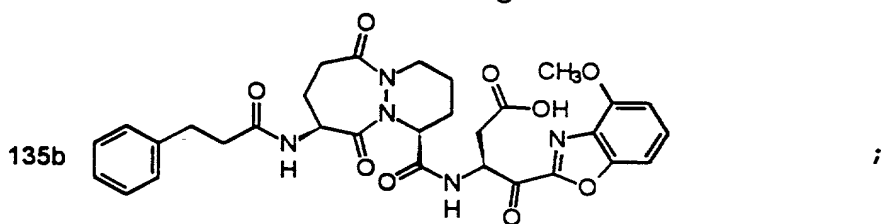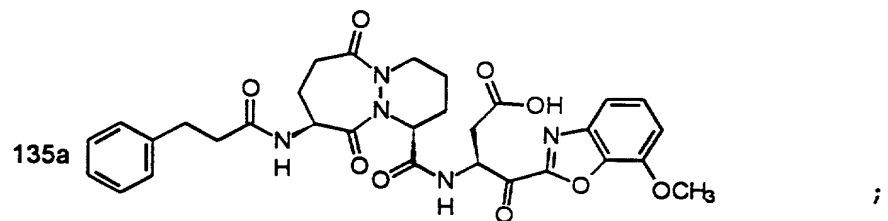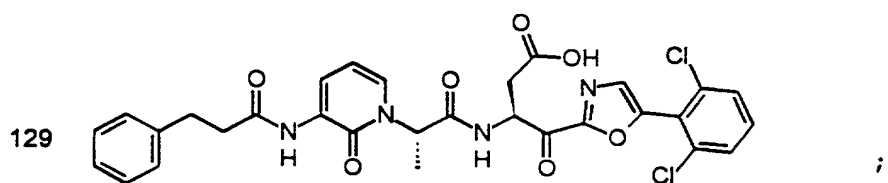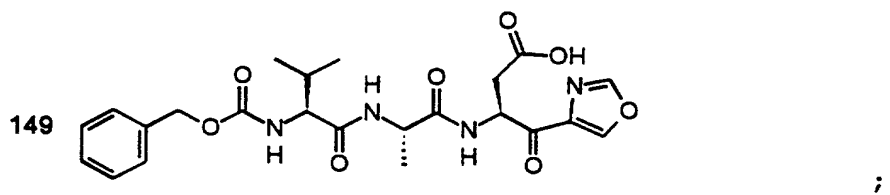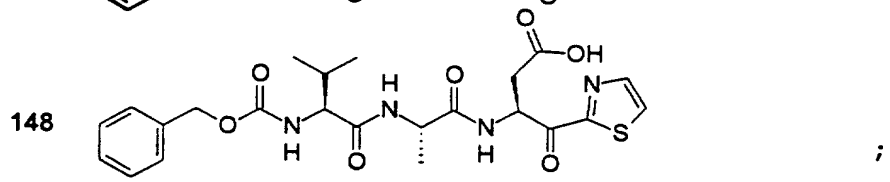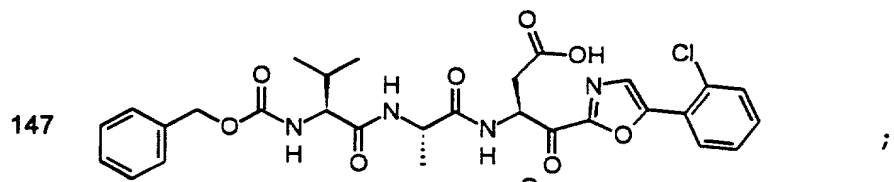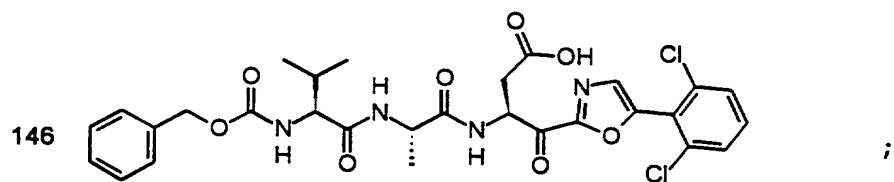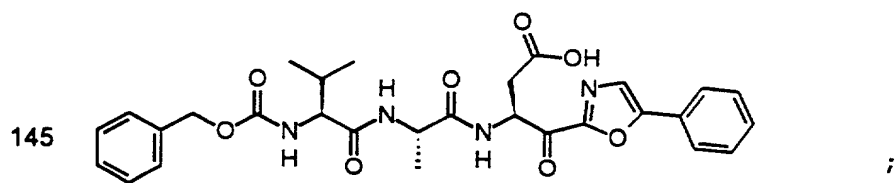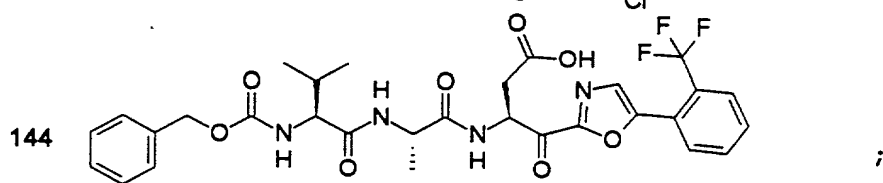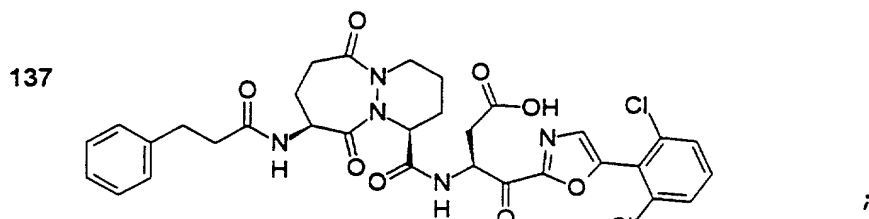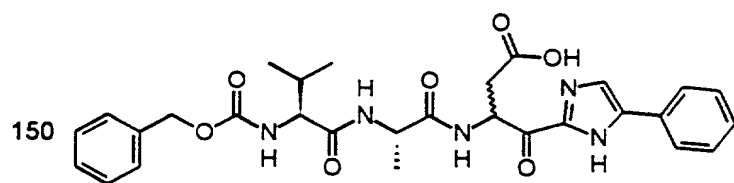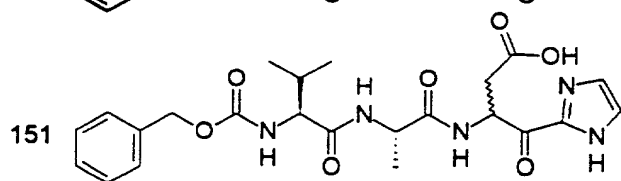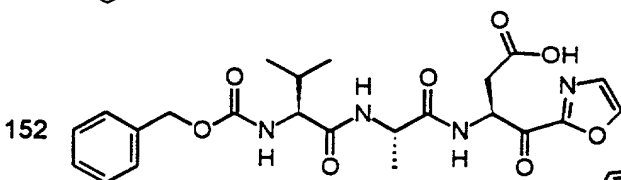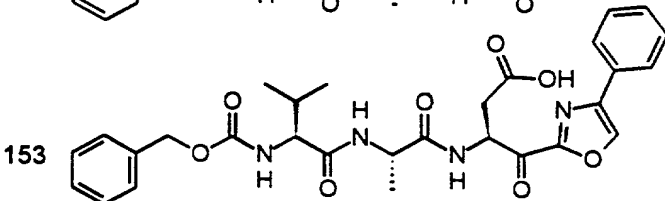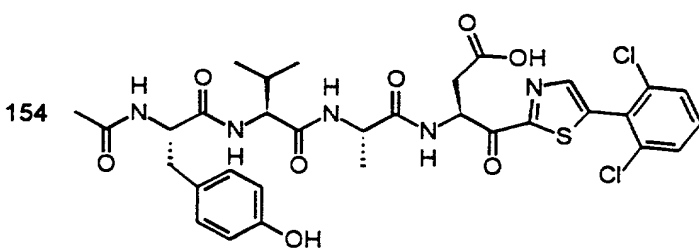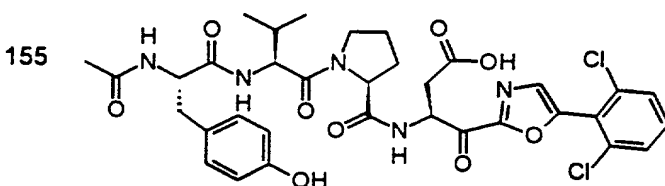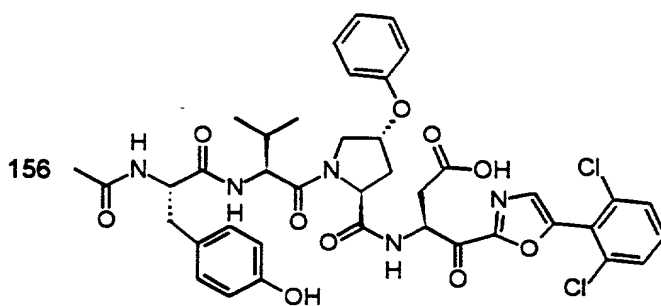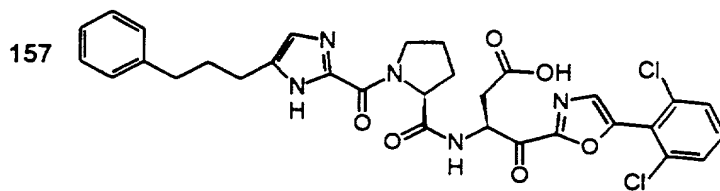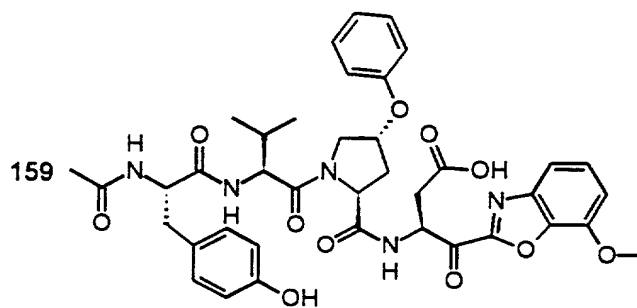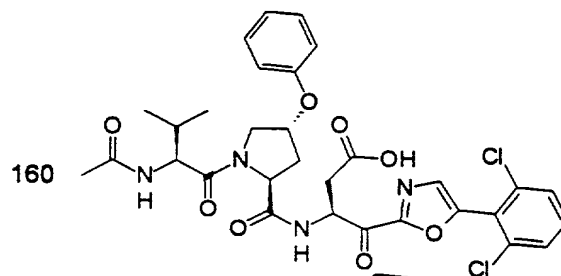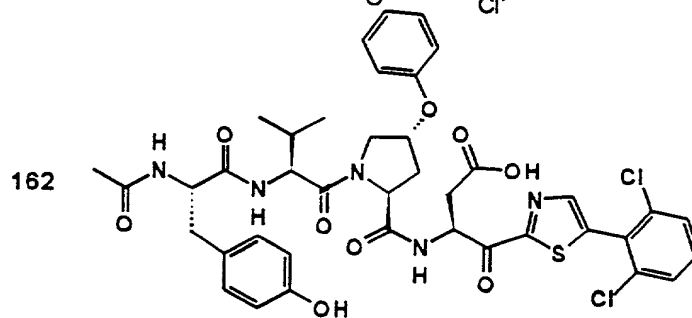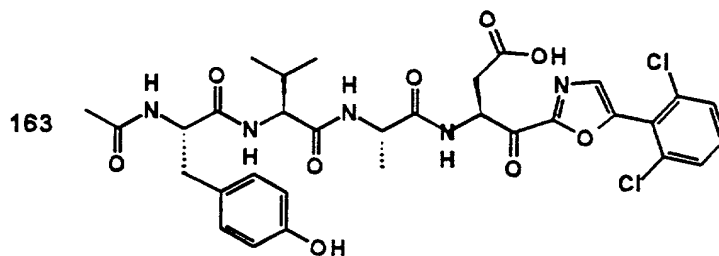
Compound 158 was synthesized by a method similar to the method used in the synthesis of (K).

158
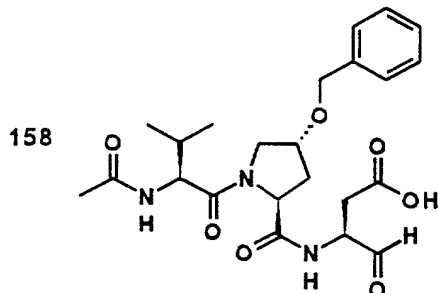
Compound 130 was synthesized by a method similar to the method used in the synthesis of 56b.

130
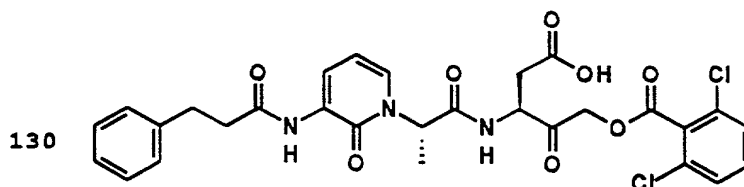
Compounds 131, 136, 138, and 142 were synthesized by a method similar to the method used in the synthesis of 57b.

131

;

136

;

138

; and

142

.

Compounds 132a, 132b, 139, 140, and 141 were synthesized by a method similar to the method used in the synthesis of 47a. The starting material for compound 140 was obtained as described in: Robl, et al., _J. Am. Chem. Soc._, 116, pp. 2348-2355 (1994). The starting material for compound 141 was obtained as described in: Wyvratt, et al., _Pept. Struct: Funct. Proc. (8th Am. Pept. Symp.)_, (1983) or USP 4415496.

132a

;

132b

;

139

;

140

; and

141

.

Compound 133 was synthesized by a method
similar to the method used in the synthesis of 47b.

133
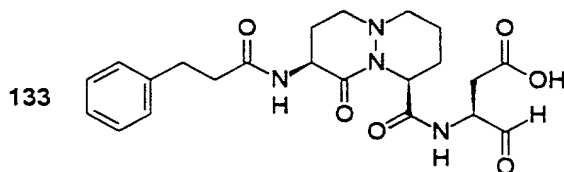
Compound 161 was synthesized by a method
similar to the method used in the synthesis of 125a.

161
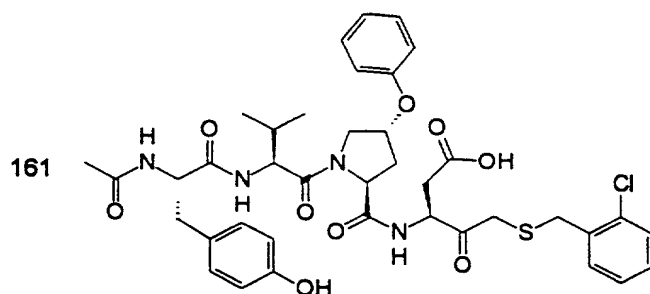
Compounds 22e, 54b, 54j, 54k, and 57b were
synthesized as described in example 5.

Compounds 85, 86, 87, 88, 89, 90, 91, 92, 98, 102a, 102b, 102c, 106a, 106b, 106c, 108a, 108b, 108c, 114a, 114b, 115, 121, 125a, and 125b were synthesized as follows.

85
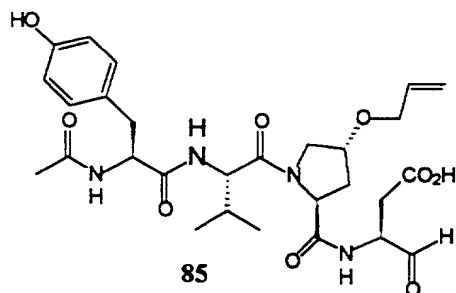
5 **N-(N-Acetyl-tyrosinyl-valinyl-(4(R)-allyloxy prolinyl))-3(S)-amino-4-oxobutanoic acid (85).**
Step A. **N-tert-Butoxycarbonyl-4(R)-allyloxyproline.** N-tert-Butoxycarbonyl(4R)-hydroxyproline (9.25 g, 40 mmol) was added to a
10 solution of 60% sodium hydride (3.36 g, 84 mmol) in 100 ml of anhydrous tetrahydrofuran and stirred for 2 hours at room temperature. Allyl bromide (6.9 ml, 80 mmol) was added to the mixture and refluxed for 6 hours. The mixture was quenched with the addition of
15 ice chips, then additional water was added and the mixture was washed with hexane. The aqueous layer was acidified with 10% sodium hydrogen sulfate and extracted with ethyl acetate (2 x 150 ml). The combined extracts were dried over anhydrous sodium
20 sulfate, filtered and evaporated to give 5 g of the title product with no further purification.

^{1}H NMR (CDCl$_3$; exist as rotamers) δ 5.92-5.82 (1H, m), 5.3-5.14 (2H, m) 4.5-4.31 (1H, m), 4.16-4.05 (1H, m), 4.04-3.9 (1H, m), 3.79-3.5 (3H, m), 2.43-2.2
25 (1.5H, m), 2.15-2.10 (0.5H, m), 1.45 (4.5H, s), 1.35 (4.5H, s).

Step B.   **4(R)-Allyloxyproline methyl ester hydrochloride.**   N-tert-Butoxycarbonyl-4(R)-allyloxyproline (5 g, 18.4 mmol) was refluxed in 50 ml of saturated methanolic hydrogen chloride for 6 hours. The mixture was evaporated in vacuo to give 3.78 g of a yellow gum as the title compound: ^{1}H NMR (CDCl$_3$) δ 5.83-5.72 (1H, m), 5.24-5.14 (1H, d), 5.13-5.08 (1H, d), 4.55-4.3 (3H, m), 4.25-4.15 (1H, m), 3.9 (1.5H, s), 3.78 (1.5H, s), 3.7-3.28 (3H, m), 2.45-2.32 (1H, m), 2.2-2.05 (1H, m).

Step C.   **N-Acetyl-tyrosinyl-valinyl-(4(R)-allyloxyproline) methyl ester.**   4(R)-Allyloxyproline methyl ester hydrochloride (1.05 g, 4.75 mmol) and N-acetyl-Tyr-Val-OH (1.68 g, 5.21 mmol) were dissolved in 10 ml of a 1:1 mixture of dichloromethane and dimethylformamide and cooled to 0 °C. Diisopropylethylamine (1 ml, 5.93 mmol) was added to the cooled mixture followed by the addition of N-hydroxybenzotriazole (0.769 g, 5.69 mmol) and 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.18 g, 6.2 mmol). After stirring for 2 hours, the mixture was warmed to room temperature and stirred for 16 hours. The reaction was poured into 150 ml of ethyl acetate and washed with 50ml each of water, 10% sodium hydrogen sulfate, and 10% sodium bicarbonate. The organic layer was dried over sodium sulfate, filtered, and evaporated to give a light yellow solid. This was purified by flash chromatography eluting with dichloromethane/methanol/pyridine (100:3:0.5) to give 780 mg of the title compound. ^{1}H NMR (CD$_3$OD) δ 7.02-6.96 (2H, d), 6.67-6.63 (2H, d), 5.95-5.85 (1H, m),

5.34-5.27 (1H, d), 5.16-5.13 (1H, d), 4.53-4.38 (3H, m), 4.28-4.22 (1H, m), 4.12-3.97 (3H, m), 3.82-3.73 (1H, m), 3.72 (3H, s), 3.04-2.88 (2H, m), 2.85-2.72 (2H, m), 2.45-2.34 (1H, m), 2.08-1.95 (2H, m), 1.92 (3H, s), 1.00-0.92 (6H, 2 x d).

Step D. **N-(N-Acetyl-tyrosinyl-valinyl-(4(R)-allyloxyprolinyl))-3(S)-amino-4-oxobutanoic acid tert-butyl ester semicarbazone.** N-Acetyl-tyrosinyl-valinyl-(4-allyloxyproline) methyl ester (770 mg, 1.57 mmol) was dissolved in 20 ml of tetrahydrofuran and 4 ml of methanol. Lithium hydroxide (145 mg, 3.46 mmol) was added to the mixture and stirred at room temperature. After two hours, 1 ml of 10% hydrogen chloride was added and the mixture evaporated in vacuo to give a solid residue then partitioned between 5ml of water and 50 ml of ethyl acetate and the organic layer separated and evaporated in vacuo to give 430 mg of the acid that waa used immediately in the next step.

N-Acetyl-tyrosinyl-valinyl-4-allyloxyproline (420 mg, 0.88 mmol) and 3-amino-4-oxobutyric acid tert-butyl ester semicarbazone (184 mg, 0.8 mol, Graybill et al., Int. J. Protein Res. , 44, pp. 173-82 (1994)) to give 100 mg (20%) of the title compound as a white amorphous solid: ^{1}H NMR (CD$_3$OD) δ 7.24-7.2 (1H, m), 7.04-6.97 (2H, d), 6.73-6.65 (2H, d), 5.98-5.86 (1H, m), 5.35-5.24 (1H, d), 5.17-5.12 (1H, m), 4.12-3.98 (2H, m), 3.72-3.67 (1H, m), 2.98-2.92 (3H, m), 2.38-2.32 (1H, m), 2.1-2.02 (2H, m), 1.92 (3H, s), 0.98-0.89 (6H, 2 x d).

Step E. **N-(N-Acetyl-tyrosinyl-valinyl-(4(R)-allyloxyprolinyl))-3(S)-amino-4-oxobutanoic acid (85).** N-(N-Acetyl-tyrosinyl-valinyl-(4(R)-allyloxyprolinyl))-3(S)-amino-4-oxobutanoic acid tert-butyl ester semicarbazone (100 mg) was deprotected as described (Example 3, compound K, Step C) to give 44.2 mg (53%) of the title compound: ^{1}H NMR (CD$_3$OD) δ 7.04-6.97 (2H, d), 6.72-6.65 (2H, d), 5.97-5.86 (1H, m), 5.32-5.25 (1H, d), 5.17-5.12 (1H, d), 4.62-4.40 (3H, m), 4.30-4.13 (2H, m), 4.12-3.96 (3H, m), 3.75-3.68 (1H, m), 2.99-2.92 (1H, m), 2.78-2.70 (1H, m), 2.70-2.48 (2H, m), 2.35-2.30 (1H, m), 2.17-1.95 (2H, m), 1.92 (3H, s), 0.98-0.88 (6H, 2 x d).

Compounds **86** and **87** were prepared by a similar method described for the synthesis of **69a** in example 5:

86
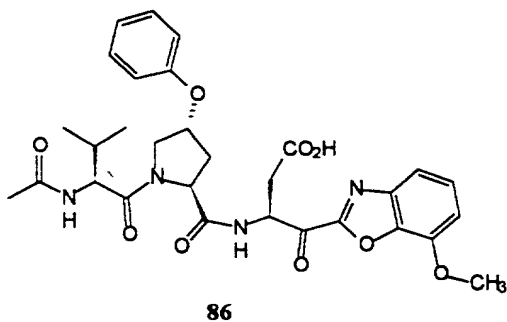
N-Acetyl-(S)-valinyl-(4-(S)-phenoxy)prolinyl-3(S)-amino-4-(7-methoxybenzoxazol-2-yl)-4-oxo-butanoic acid (86). N-Acetyl-(S)-valinyl-(S)-(4-(S)-phenoxy)proline was converted to **86** as a white powder: ^{1}H NMR (DMSO-d$_6$) δ 8.75(d, 1H), 7.6-7.2(m, 4H), 7.0-6.8(m, 4H), 5.5(m, 1H), 5.05(s, 1H), 4.5(t,

1H), 4.29(t, 1H), 4.0(s, 3H), 4.0-3.8(m, 2H), 3.0-2.8(dd, 2H), 2.3(m, 1H), 2.09(m, 1H), 1.95-1.8(m, 2H), 1.78(s, 3H), 1-0.7(dd, 6H).
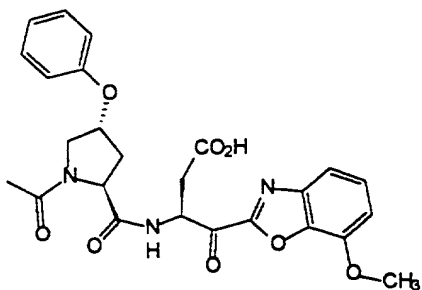
87

N-Acetyl(4-(R)-phenoxy)prolinyl-3(S)-amino-4-(7-methoxybenzoxazol-2-yl)-4-oxo-butanoic acid (87): N-Acetyl-(S)-(4-(S)-phenoxy)proline was converted to **87** as a white powder: ^{1}H NMR (DMSO-d$_6$) δ 9.1(d, 1H), 8.76(d, 1H), 7.6-7.2(m, 4H), 7.0-6.9(m, 4H), 5.55(m, 1H), 5.45(m, 1H), 5.0(m, 2H), 4.56(t, 1H), 4.40(t, 1H), 4.0(s, 3H), 3.9(dd, 1H), 3.76(d, 1H), 3.64(d, 1H), 3.1-2.9(m, 1H), 2.8(m, 1H), 2.50(m, 1H), 2.3-2.2(m, 1H), 2.09(m, 1H), 1.95 and 1.75(2 x s, 3H, rotamers)
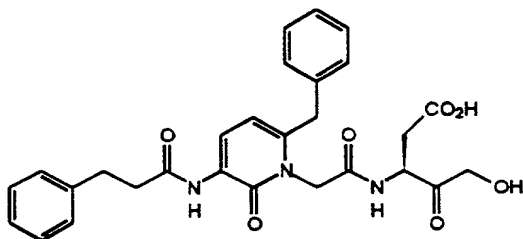
88

N-2-(6-Benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl) acetyl-3(S)-amino-5-hydroxy-4-oxo-pentanoic acid (88). N-2-(6-Benzyl-

1,2-dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-
pyridyl) acetyl-3(S)-amino-5-hydroxy-4-oxo-pentanoic
acid tert-butyl ester was prepared from **52b** and **81**
following the method described for the synthesis of
5   **83a** to give a white solid (45%): ^{1}H NMR(CDCl$_3$) δ
8.40(d, 1H), 8.20(s, 1H), 7.4-7.1(m, 11H), 6.18(s,
1H), 4.72(m, 1H), 4.65-4.5(q, 2H), 4.4-4.2(dd, 2H),
4.0(s, 2H), 3.04(t, 2H), 2.9(dd, 1H), 2.76(t, 2H),
2.55(dd, 1H), 1.39(s, 9H).
10   The resulting product was converted to **88** by method
described in example 5, compound **84a** to give the
title compound (42%) as a white solid: ^{1}H NMR(CDCl$_3$)
δ 8.5(d, 1H), 8.1(d, 1H), 8.0(m, 1H), 7.4-7.1(m,
11H), 6.3(d, 1H), 4.9-4.8(m, 2H), 4.6-4.4(m, 2H),
15   4.3(dd, 1H), 4.1(s, 2H), 3.3(t, 1H), 3.05(t, 2H),
2.8-2.6(m, 3H)

Compounds **89** and **90** were prepared by a similar method
described for the preparation of **84a** in example 5.

20

89
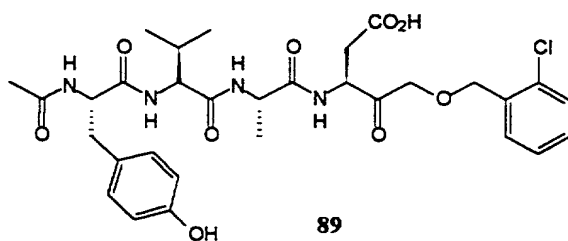
**N-Acetyl-(S)-tyrosinyl-(S)-valinyl-(S)-alaninyl-3(S)-
amino-5-(2-chlorobenzyloxy)-4-oxo-pentanoic acid
(89)**was prepared from Ac-Tyr-Val-Ala-OH and (3S) t-
25   butyl N-(allyloxycarbonyl)-3-amino-5-(2-chlorophenyl-
methoxyl)-4-oxo-pentanoate (prepared by a similar
method as **82**) to give a white solid: ^{1}H NMR (DMSO-

d_6) δ 9.15(s, 1H), 8.5(d, 1H), 7.98(d, 1H), 7.75(d, 1H), 7.55-7.3(m, 4H), 7.0(d, 1H), 6.6(d, 2H), 4.6-4.3(m, 6H), 4.3-4.1(m, 2H), 2.9(d, 1H), 2.76(dd, 1H), 2.7-2.5(m, 2H), 1.95(m, 1H), 1.75(s, 3H), 1.2(d, 3H), 0.9-0.7(dd, 6H)
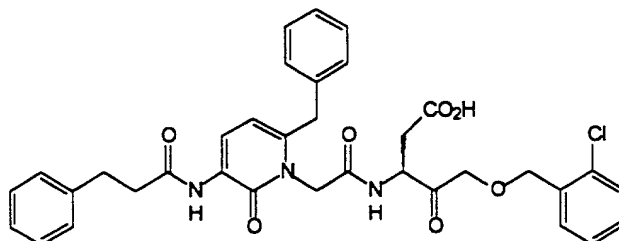
90

N-2-(6-Benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl) acetyl-3-amino-5-(2-chlorobenzyloxy)-4-oxo-pentanoic acid (90) was prepared from **52b** and (3S) t-butyl N-(allyloxycarbonyl)-3-amino-5-(2-chlorophenyl-methoxyl)-4-oxo-pentanoate (prepared by a similar method as **82**) to give a white solid: ^{1}H NMR(DMSO-d_6) δ 9.2(s, 1H), 8.75(d, 1H), 7.7-7.1(m, 14H), 6.4(d, 1H), 4.65(d, 6H), 4.56(s, 1H), 4.6-4.35(dd, 1H), 3.9(s, 2H), 2.9-2.6(m, 6H)

91
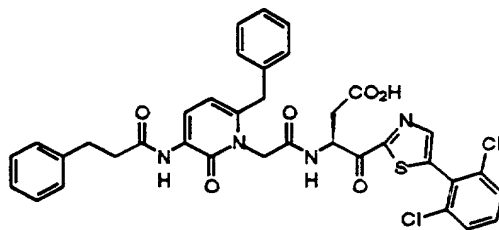
N-2-(6-Benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl) acetyl-3(S)-amino-5-(5-(2,6-dichlorophenyl) thiazol-2-yl)-4-oxo-pentanoic

acid (91) was prepared from 52b and 3-
(Allyloxycarbonyl)-amino-4-[(2,6-dichloro-phenyl)-
thiazol- 2-yl]-4-hydroxy-butyric acid tert-butyl
ester (99) as described for the preparation of 69a to
give an off-white powder: ^{1}H NMR(DMSO-d$_6$) δ 9.32(s,
1H), 9.05(d, 1H), 8.27(d, 1H), 8.18(d, 1H), 7.7(d,
1H), 7.6(t, 1H), 7.4-7.1(m 11H), 6.1(d, 1H), 5.64(m,
1H), 4.8-4.6(dd, 2H), 3.85(s, 2H), 3.02(m, 1H), 2.9-
2.7(m, 4H).
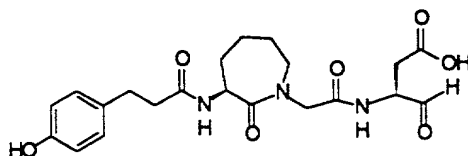
92

3-(S)-(2-(3[3-(S)-(4-Hydroxy-phenyl)-propionylamino]-
2-oxo-azepan-1-yl)-acetylamino)-4-oxo-butyric acid
(92) was prepared from 2-(3[3-(S)-(4-Hydroxy-phenyl)-
propionylamino]-2-oxo-azepan-1 -yl)-acetic acid and
N-allyloxycarbonyl-4-amino-5-benzyloxy-2-
oxotetrahydrofuran (Chapman, Biorg. Med. Chem. Lett.,
2, pp. 613-18 (1992)) by a similar method described
for the synthesis of 54a to give the title compound
as a white solid: ^{1}H NMR(DMSO-d$_6$) δ 9.10-9.20(s, 1H),
8.40(s, 1H), 7.88(d, 1H), 7.0(d, 2H), 6.64(d, 2H),
4.60(t, 1H), 4.10(q, 2H), 3.9-4.2(m, 2H), 3.6(m, 1H),
3.18(d, 2H), 2.70(t, 2H), 2.40(m, 2H), 1.85-1.40(m,
8H).
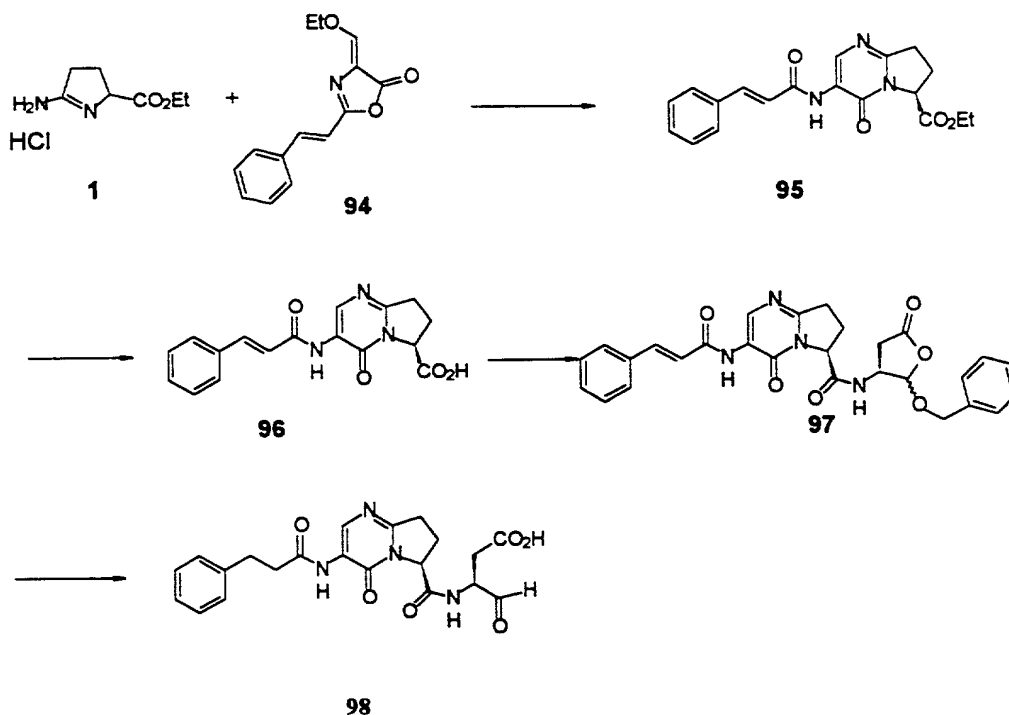
4-Ethoxymethylene-2-styryl-4H-oxazol-5-one (94) was prepared according to Cornforth, _The Chemistry of Penicillin._ Clarke, Johnson, Robinson, (eds.)
5   Princeton University Press, p. 804 (1949)

4-Oxo-3-(3-phenyl-acryloylamino)-4,6,7,8-tetrahydro-pyrrolo[1,2-a]pyrimidine-(6S)-carboxylic acid ethyl ester (95) was prepared from **94** by the procedure in example 5 for compound **3** to give 4.5g (30%) of the
10   title compound: ^{1}H NMR (CD$_3$OD) δ 1.3 (t, 3H), 2.35 (m, 1H), 2.65 (m, 1H), 3.1 (m, 1H), 3.15 (m, 1H), 4.25 (q, 2H), 5.15 (dd, 1H), 6.95 (d, 1H), 7.4 (m, 3H), 7.6 (m, 2H), 7.65 (d, 1H), 8.95 (s, 1H).

4-Oxo-3-(3-phenyl-acryloylamino)-4,6,7,8-tetrahydro-pyrrolo[1,2-a]pyrimidine-(6S)-carboxylic acid (96) A mixture of 4-Oxo-3-(3-phenyl-acryloylamino)-4,6,7,8-tetrahydro-pyrrolo[1,2-a]pyrimidine-(6S)-carboxylic acid ethyl ester (**95**, 3.1g, 8.8mmol) and aqueous 1N lithium hydroxide (8.8mL, 8.8mmol) in methanol (10mL) was stirred 18h at room temperature. The reaction was diluted with water and washed with ethyl ether (1 x 20mL). The aqueous layer was acidified with conc. hydrochloric acid. The solid was collected by filtration and washed with water. The solid was dried in a vacuum oven at 50 °C for 18h to give 2.2g (75%) of the title compound as a tan solid: ^{1}H NMR(CD$_3$OD) δ 2.4(m 1H), 2.7(m, 1H), 3.1(m, 1H), 3.2(m, 1H), 5.15(dd, 1H), 7.0(d, 1H), 7.4(m, 3H), 7.6(m, 2H), 7.65(d, 1H), 8.95(s, 1H)

4-Oxo-3-(3-phenyl-acryloylamino)-4,6,7,8-tetrahydro-pyrrolo[1 ,2-a]pyrimidine-(6S)-carboxylic acid (2-benzyloxy-5-oxo-tetrahydro-furan-(3S)-yl)-amide (97) was prepared from **96** by the method described in example 3 for compound **H**, step A to give 0.52g (75%) of the title compound as a mixture of diastereomers: ^{1}H NMR(CDCl$_3$) δ 2.3-2.7(m, 3H), 2.9(dd, 1H), 3.05(m, 1H), 3.3(m, 1H), 4.4-4.8(m, 2H), 4.9(2 x d, 1H), 5.05(m, 1H), 5.55(2 x s, 1H), 6.6(2 x d, 1H), 7.4(m, 6H), 7.55(m, 4H), 7.65(2 x d, 1H), 8.0(m, 2H), 9.2(s x 2, 1H).

4-Oxo-(3S)-{[4-oxo-3-(3-phenyl-propionylamino)-4,6,7,8-tetrahydro-pyrrolo[1,2-a]pyrimidine-(6S)-carbonyl]-amino}-butyric acid (98) was prepared by the procedure in example 3 for compound **H**, step D to

give 0.13g (45%) of the title compound: ^{1}H
NMR(CD$_3$OD) δ 2.35(m, 1H), 2.45-2.75(m, 3H), 2.8(t,
2H), 3.0(t, 2H), 3.1(m, 1H), 3.25(m, 1H), 4.3(m, 1H),
6.65(dd, 1H), 5.15(m, 1H), 7.15(m, 1H), 7.3(m, 4H),
5   8.8(a,1H).

58   **99**
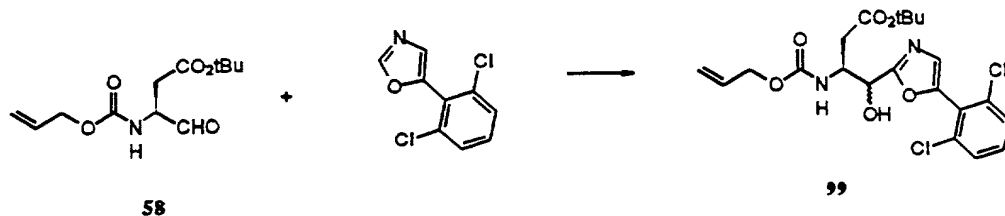
**3(S)-(Allyloxycarbonyl)-amino-4-[(2,6-dichloro-
phenyl)-oxazol-2-yl]-4(R,S)-hydroxy-butyric acid
tert-butyl ester (99).** A solution of 5-(2,6-
Dichlorophenyl)oxazole (2.71g, 12.7mmol; prepared by
10   a similar method described in Tet. Lett. 23, p2369
(1972)) in tetrahydrofuran (65mL) was cooled to -78
°C under a nitrogen atmosphere. To this solution was
added n-butyl lithium (1.5M solution in hexanes,
8.5mL, 13.3mmol) and stirred at -78 °C for 30min.
15   Magnesium bromide etherate (3.6g, 13.9mmol) was added
and the solution was allowed to warm to -45 °C for
15min. The reaction was cooled to -78 °C and
aldehyde **58** (3.26g, 12.7mmol; Graybill et al., <u>Int.
J. Protein Res.</u>, 44, pp. 173-182 (1993)) in
20   tetrahydrofuran (65mL) was added dropwise. The
reaction was stirred for 25min., then allowed to warm
to -40 °C and stirred for 3h, and then at room
temperature for 1h. The reaction was quenched with
5% NaHCO$_3$ (12mL) and stirred for 3h. The
25   tetrahydrofuran was removed in vacuo and the
resulting residue was extracted with dichloromethane.
The organic layer was washed with saturated sodium
chloride solution and dried over magnesium sulfate,

filtered, and concentrated to yield 6.14g of the title compound. Purification gave 4.79g (80%) of **99**: ^{1}H NMR (CDCl$_3$) δ 1.45(s, 9H), 2.7-2.5(m, 2H), 2.8(dd, 1H), 4.2, 4.4(2 x d, 1H), 4.7-4.5(m, 3H), 5.35-5.1(m, 2H), 5.6, 5.7(2 x d, 1H), 6.0-5.8(m, 1H), 7.2(d, 1H), 7.3(m, 1H), 7.4(m, 2H).

4-Oxo-3-(3-phenyl-propionylamino)-4,6,7,8-tetrahydro-pyrrolo [1,2-a]pyrimidine-(6S)-carboxylic acid (100). A mixture of 4-Oxo-3-(3-phenyl-acryloylamino)-4,6,7,8-tetrahydro-pyrrolo[1,2-a]pyrimidine-(6S)-carboxylic acid (**96**; 2.1g, 6.5mmol) and 20% palladium hydroxide on carbon (0.5g) in methanol (50mL) was stirred under a hydrogen atmosphere for 4h. The resulting mixture was filtered and concentrated to yield 2.1g (100%) of the title compound as a white solid: ^{1}H NMR(CD$_3$OD) δ 2.35(m, 1H), 2.65(m, 1H), 2.75(t, 2H), 3.0(t, 2H), 3.1(m, 1H), 3.15(m, 1H), 5.1(dd, 1H), 7.15(m, 1H), 7.25(m, 4H), 8.75(s, 1H)

96

100

101

102

a R =

b R =

c R =
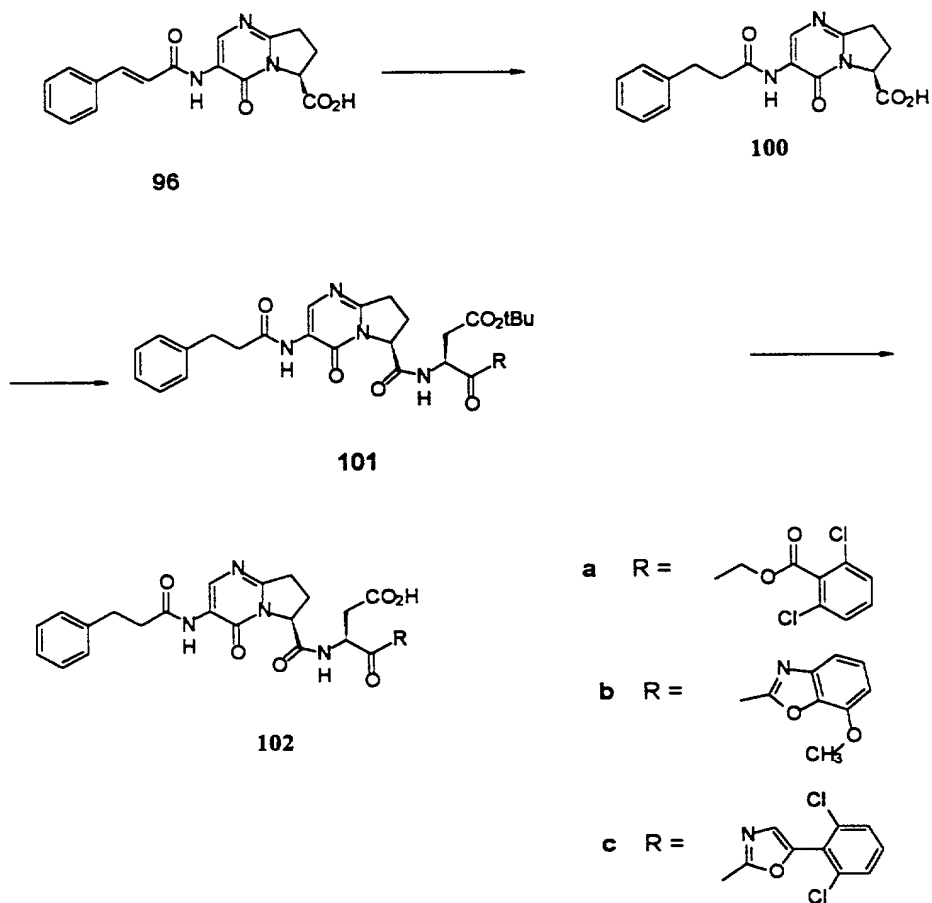
2,6-Dichloro-benzoic acid 4-tert-butoxycarbonyl-2-oxo-(3S)-{[4-oxo-3-(3-phenyl-propionylamino)-4,6,7,8-tetrahydro-pyrrolo[1,2-a]pyrimidine-(6S)-carbonyl]-amino}-butyl ester (101a) was prepared by the procedure in example 5 for compound **56a** to give 0.16g

5   (20%) of the title compound: ^{1}H NMR(CD$_3$OD) δ 1.45(s, 9H), 2.3(m, 1H), 2.6(m,1H), 2.7(m, 3H), 2.95(m, 3H), 4.8(m, 1H), 5.1(m, 1H), 5.2(q, 2H), 7.1(m, 1H), 7.2(m, 4H), 7.4(m, 3H), 8.75(s, 1H).

4-(7-methoxy-benzoxazol-2-yl)-4-oxo-(3S)-{[4-oxo-3-

10   (3-pheny l-propionylamino)-4,6,7,8-tetrahydro-pyrrolo[1,2-a]pyrimidine-(6S)-carbonyl]-amino}-butric

acid tert-butyl ester (101b). 4-Hydroxy-4-(7-
methoxy-benzoxazol-2-yl)-(3S)-{[4-oxo-3-(3-phenyl-
propionylamino)-4,6,7,8-tetrahydro-pyrrolo[1,2-
a]pyrimidine-(6S)-carbonyl]-amino}-butyric acid tert-
butyl ester was prepared from **100** and **66a** by the
procedure in example 5 for compound **67a** to give 0.95g
(quantitative) of the product as a mixture of
diastereomers: ^{1}H NMR(CD$_3$OD) δ 1.45(2 x s, 9H), 2.2(2
x m, 1H), 2.35-3.0(m, 9H), 4.0(m, 3H), 4.75(m,1H),
4.85(m, 1H), 5.05(2 x dd, 1H), 7.1(2 x dd, 1H), 7.15-
7.3(m, 4H), 7.5(2 x t, 1H), 7.8(2 x d, 1H), 8.55(2 x
dd, 1H), 8.7(2 x s, 1H).
The resulting product was converted to **101b** by the
procedure in example 5 for compound **68a** to give
0.36g (50%) of the title compound: ^{1}H NMR(CD$_3$OD) δ
1.4(s, 9H), 2.35(m, 1H), 2.55(m, 1H), 2.75(t, 2H),
2.95(t, 2H), 3.00(m,1H), 3.1(dd, 2H), 3.15(m, 1H),
5.15(dd, 1H), 5.65(t, 1H), 7.1(m, 2H), 7.2(m, 4H),
7.4(m, 2H), 8.7(s, 1H)

**4-[5-(2,6-Dichloro-phenyl)-oxazol-2-yl]-4-oxo-(3S)-
{[4-oxo-3-(3- phenyl-propionylamino)-4,6,7,8-
tetrahydro-pyrrolo[1,2-a]pyrimidine-(6S)-carbonyl]-
amino}-butyric acid tert-butyl ester (101c).** 4-[5-
(2,6-Dichloro-phenyl)-oxazol-2-yl]-4-hydroxy-(3S)-
{[4-oxo-3-(3-phenyl-propionylamino)-4,6,7,8-
tetrahydro-pyrrolo[1 ,2-a]pyrimidine-(6S)-carbonyl]-
amino}-butyric acid tert-butyl ester from **100** and **99**
using the method described in example 5, compound **67a**
to give 0.09g (60%) of the product as a mixture of
diastereomers: ^{1}H NMR(CD$_3$OD) δ 1.45(2 x s, 9H),
2.2(m, 1H), 2.5(m, 2H), 2.7(2 x dd, 1H), 2.75(t, 2H),

2.9-3.1(m, 4H), 4.7(m, 1H), 5.1(m, 2H), 7.1(m, 1H), 7.1-7.25(m, 4H), 7.4(t, 1H), 7.5(t, 1H), 8.55(d, 1H), 8.75(s, 1H).

The resulting product was converted to **101c** by the method described in example 5, compound **68a** to give 0.04g (45%) of the title compound: ^{1}H NMR(CD$_3$OD) δ 1.4(s, 9H), 2.3(m, 1H), 2.6(m, 1H), 2.75(t, 2H), 2.95(t, 2H), 2.9-3.2(m, 4H), 5.2(dd, 1H), 5.55(t, 1H), 7.1(m, 1H), 7.25(m, 4H), 7.55(m, 3H), 8.75(s, 1H).

2,6-Dichloro-benzoic acid 4-carboxy-2-oxo-(3S)-{[4-oxo-3-(3-phenyl-propionylamino)-4,6,7,8-tetrahydro-pyrrolo[1,2-a]pyrimidine-(6S)-carbonyl]-amino}-butyl ester (102a) was prepared from **101a** by the procedure in example 5 for compound **57a** to give 0.12g (80%) of the title compound: ^{1}H NMR(CD$_3$OD) δ 2.35(m, 1H), 2.65(m, 1H), 2.75(m, 2H), 2.85(dd, 1H), 2.95(m, 2H), 3.0(dd, 1H), 3.15(m, 1H), 3.25(m, 1H), 4.55(dd, 1H), 5.15(m, 1H), 5.25(q, 2H), 7.15(m, 1H), 7.25(m, 4H), 7.45(m, 1H), 8.8(s, 1H).

4-(7-methyoxy-benzoxazol-2-yl)-4-oxo-(3S)-{[4-oxo-3-(3-phenyl-propionylamino)-4,6,7,8-tetrahydro-pyrrolo [1,2-a]pyrimidine-(6S)-carbonyl]-amino}-butric acid (102b) was prepared from **101b** by the procedure described in example 5 for compound **69a** to give 0.12g (35%) of the title compound: ^{1}H NMR(DMSO-d$_6$) δ 2.1(m, 1H), 2.55(m, 1H), 2.7-3.1(m, 8H), 4.05(s, 3H), 5.1(dd, 1H), 5.55(t, 1H), 7.2(m, 1H), 7.25(m, 5H), 7.5(t, 1H), 7.55(d, 1H), 8.7(s, 1H), 9.2(d, 1H), 9.4(s, 1H), 12.7(br, 1H).

4-[5-(2,6-Dichloro-phenyl)-oxazol-2-yl]-4-oxo-(3S)-
{[4-oxo-3 -(3-phenyl-propionylamino)-4,6,7,8-
tetrahydro-pyrrolo[1,2-a] pyrimidine-(6S)-carbonyl]-
amino}-butyric acid (102c) was prepared from 101c as
described in example 5 for compound 69a to give 0.01g
(40%) of the title compound: ^{1}H NMR(CD$_3$OD) δ 2.35(m,
1H), 2.6(m, 1H), 2.75(t, 2H), 2.95(t, 2H), 3.05(m,
1H), 3.15(m, 3H), 5.15(dd, 1H), 5.55(t, 1H), 7.15(m,
1H), 7.2(m, 4H), 7.55(m, 3H), 8.8(s, 1H)
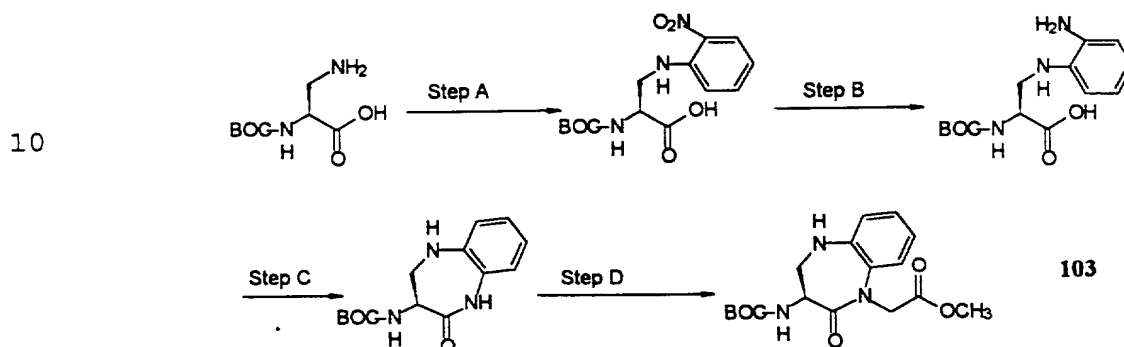
(3-*tert*-Butoxycarbonylamino-2-oxo-2,3,4,5-tetrahydro-
benzo[b][1,4]diazepin-1-yl)acetic acid methyl ester
(103).

Step A. 2(S)-*tert*-Butoxycarbonylamino-3-(2-
nitrophenyl-amino)-propionic acid. 2-*tert*-
Butoxycarbonylamino-3-aminopropionic acid (10 g, 49
mmol), 2-fluoronitrobenzene (5.7 ml, 54 mmol), and
sodium bicarbonate (8.25 g, 98 mmol) was taken into
130 ml of dimethylformamide and heated at 80 °C for
18 hours. The reaction was evaporated in vacuo to
give a viscous orange residue that was dissolved in
300 ml of water and extracted with diethyl ether (3 x
150 ml). The aqueous solution was acidified to pH 5
with 10 % sodium hydrogen sulfate and extracted with

ethyl acetate (3 x 250 ml). The combined extracts
were dried over anhydrous sodium sulfate, filtered,
and evaporated to give 12.64 g (83 %) of the title
compound as an orange amorphous solid. ^{1}H NMR (CD$_3$OD)

5   δ 8.15-8.10 (1H,d), 7.54-7.48 (1H,t), 7.13-7.08 (1H,
d), 6.73-6.65 (1H, t), 4.45-4.35 (1H, m), 3.9-3.8
(1H, dd), 3.65-3.55 (1H, dd), 1.45 (9H, s).

**Step B.   2(S)-*tert*-Butoxycarbonylamino-3-(2-
aminophenyl-amino)-propionic acid.** A mixture of 2-

10   tert-Butoxycarbonylamino-3-(2-
nitrophenylamino)propionic acid (12.65 g, 40.5 mmol)
and 0.5 g of 10% Pd/C in 100 ml of methanol under
hydrogen at 1 atmosphere was stirred for 4 hrs. The
solution was filtered through Celite 545 and the

15   filtrate evaporated in vacuo to afford 11.95 g of the
title compound in quantitative yield as a dark brown
solid that was used without purification. ^{1}H NMR
(CD$_3$OD) δ 6.75-6.70 (3H,m), 6.65-6.58 (1H, m), 4.35-
4.3 1H, m), 3.6-3.38 (2H, m), 1.45 (9H, s).

20   **Step C.   3(S)-*tert*-Butoxycarbonylamino-1,3,4,5-
tetrahydro-benzo[b][1,4] diazepin-2-one.** 1-(3-
Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
(8.54 g, 44.5 mmol) was added to a cooled (0 °C)
solution of 2-*tert*-butoxycarbonylamino-3-(2-

25   aminophenylamino)propionic acid (11.95 g, 40.5 mmol)
in 100 ml of dimethylformamide and stirred for 18
hours. The reaction was poured into 700 ml of ethyl
acetate and washed four times with 100 ml of water.
The organic layer was dried over anhydrous sodium

30   sulfate, filtered, and evaporated to give a brown
solid that was purified by flash chromatography

eluting with 3:7 ethyl acetate/hexane to give 8 g

(71%) of the title compound: ^{1}H NMR (CDCl$_3$) δ 7.78 (1H,

s), 7.02-6.95 (1H, m), 6.88-6.82 (1H, m), 6.82-6.78

(1H, m), 6.75-6.70 (1H, m), 5.8-5.7 (1H, d), 4.55-4.45

5   (1H, m), 3.95 (1H, s), 3.9-3.82 (1H, m), 3.48-3.40

(1H,m), 1.45 (9H,s).

Step D.   **(3(S)-*tert*-Butoxycarbonylamino-2-oxo-**
2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl)acetic
acid methyl ester (103).   A 1.0 M solution of lithium

10   bis(trimethylsilyl)amide (3.4 ml, 3.4 mmol) in THF was
added dropwise to a -78 °C solution of 3-*tert*-
butoxycarbonylamino-1,3,4,5-
tetrahydrobenzo[b][1,4]diazepin-2-one (0.94 g, 3.38
mmol) in 20 ml of anhydrous tetrahydrofuran and

15   stirred for 30 minutes. Methyl bromoacetate (o.44 ml,
4 mmol) was added dropwise to the reaction mixture
then warmed to room temperature. The reaction was
diluted with 100 ml of ethyl acetate and washed with
0.3N potassium hydrogen sulfate (50 ml), water (2 x 50

20   ml), and brine. The combined organics were dried over
anhydrous sodium sulfate, filtered, and evaporated to
afford a gum that was purified by flash chromatography
eluting with 3:7 EtOAc/Hex. to give 0.98 g (83%) of
the title compound as a white solid. ^{1}H NMR (CDCl$_3$) δ

25   7.15-7.07 (2H, m), 6.98-6.94 (1H, m), 6.88-6.84 (1H,
d), 5.62-5.55 (1H, d), 4.71-4.65 (1H, d), 4.65-4.6
(1H, m), 4.33-4.27 (1H, d), 3.96-3.90 (1H, m), 3.78
(3H, s), 3.44-3.37 (1H, m), 1.4 (9H, s).
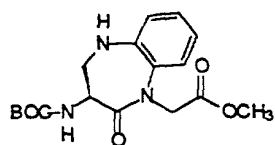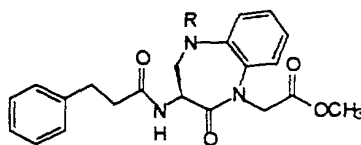
103 → **104**
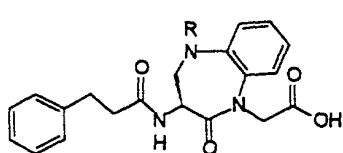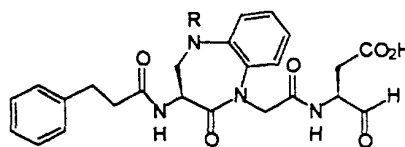
105 → **106**

a R = H
b R = COCH₂CH₂Ph
c R = CH₂Ph

[2-Oxo-3(S)-(3-phenylpropionylamino)-2,3,4,5-tetrahydro-benzo[b] [1,4]diazepin-1-yl]acetic acid methyl ester (104a). Anhydrous hydrogen chloride was bubbled into a solution of (3(S)-*tert*-butoxycarbonylamino-2-oxo-2,3,4,5-tetrahydro-benzo[b] [1,4]diazepin-1-yl)acetic acid methyl ester (**103**, 1g, 2.86 mmol) in 25 ml of ethyl acetate for 2 minutes then stirred for 1 hour at room temperature. The reaction was evaporated to give 2-oxo-3(S)-amino-2,3,4,5-tetrahydrobenzo[b] [1,4]diazepin-1-yl acetic acid methyl ester hydrochloride as a white solid. The hydrochloride salt and hydrocinnamic acid (0.47 g, 3.15 mmol) was dissolved into 20 ml of dimethylformamide and cooled to 0 °C. Diisopropylethylamine (1 ml, 5.72 mmol) was added to the solution followed by the addition of N-hydroxybenzotriazole and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride. After stirring for

18 hours at room temperature, the mixture was diluted with 150 ml of ethyl acetate and washed with 10% sodium hydrogen sulfate, 10% sodium bicarbonate, and brine. The organic layer was dried over anhydrous sodium sulfate, filtered, and evaporated to a crude solid that was purified by flash chromatography eluting with 7:3 ethyl acetate/dichloromethane to afford 600 mg (55%)of the title compound as a white solid. ^{1}H NMR (CDCl$_3$) δ 7.3-6.85 (9H,m), 6.55-6.0 (1H, d), 4.88-4.82 (1H, m), 4.72-4.65 (1H, d), 4.28-4.22 (1H, m), 3.95-3.9 (1H, m), 3.78 (3H, s), 3.65 (1H, br. s), 3.28-3.2 (1H, m), 2.95-2.84 (2H, m), 2.55-2.4 (2H, m).

(3(S)-(3-Phenylpropionylamino)-2-oxo-2,3,4,5-tetra-hydrobenzo[b][1,4]diazepin-1-yl)acetic acid (105a).
(3(S)-(3-Phenylpropionylamino)-2-oxo-2,3,4,5-tetrahydro-benzo[b][1,4]diazepin-1-yl)acetic acid methyl ester (**104a**) was dissolved in 90% methanol. Lithium hydroxide hydrate was added to the reaction and the reaction was stirred at room temperature for 4 h. The reaction was evaporated in vacuo to give a white solid. This was dissolved in 20 ml of water and acidified to pH 5 and extracted with ethyl acetate to afford 304 mg (88%) of the title compound as a white solid. ^{1}H NMR (CDCl$_3$) δ 7.5-6.9 (11H, m), 4.92-4.8 (1H, m), 4.7-4.58 (1H, d), 4.38-4.25 (1H, d), 3.88-3.78 (1H, m), 3.45-3.25 (1H, m), 3.05-2.85 (2H, m), 2.55-2.45 (2H, m).

4-Oxo-3(S)-{2-[2-oxo-3(S)-(3-phenylpropionylamino)-2,3,4,5-tetrahydro-benzo[b][1,4]diazepin-1-ylacetylamino}butyric acid (106a). N-[1-(2-Benzyloxy-

5-oxotetrahydrofuran-3-ylcarbamoyl-methyl)- 2-oxo-
2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-3-
phenylpropionamide was prepared from **105a** by the
procedure in example 3, compound **H** (stepA) to afford
390 mg (93%) of the product as diastereomers. ^{1}H NMR
(CD$_3$OD) δ 7.58-7.22 (14H, m), 5.78-5.73 (0.5 H, d),
5.64 (0.5 H, s), 5.0-4.72 (4H, m), 4.54-4.42 (2H, m),
3.82-3.76 (0.5 H, m), 3.68-3.62 (o.5 H, m), 3.28-3.21
(0.5H, m), 3.19-3.12 (0.5H, m), 3.07-2.98 (2H, m),
2.78-2.48 (4H, m).

The resulting product was converted to **106a** by the
method described in example 3, compound **H** (StepD) to
afford the title compound as a white solid (17%): ^{1}H
NMR (CD$_3$OD) δ 7.54-6.98 (9H, m), 5.58-5.44 (1H, m),
4.8-4.2 (4H, m), 3.96-3.3 (2H, m), 3.30-3.05 (1H, m),
2.98-2.25 (5H, m).

[2-Oxo-5-(3-phenylpropionyl)-3(S)-(3-
phenylpropionylamino)-2,3,4,5-
tetrahydrobenzo[b][1,4]diazepin-1-yl]acetic acid
methyl ester (104b). Anhydrous hydrogen chloride was
bubbled into a solution of (3(S)-*tert*-
butoxycarbonylamino-2-oxo-2,3,4,5-tetrahydro-
benzo[b][1,4]diazepin-1-yl)acetic acid methyl ester
(**103**, 1g, 2.86mmol) in 25 ml of ethyl acetate for 2
minutes then stirred for 1 hour at room temperature.
The reaction was evaporated to give 2-oxo-3(S)-amino-
2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl acetic
acid methyl ester hydrochloride as a white solid.
The hydrochloride salt was suspended into 20 ml of
dichloromethane and cooled to 0 °C. Triethylamine
(1.6 ml, 11.5 mmol) was added to the suspension
followed by the dropwise addition of dihydrocinnamoyl

chloride (0.9 ml, 6 mmol). The mixture was warmed to room temperature and stirred for 18 hours. The mixture was diluted with 25 ml of dichloromethane and washed twice with 50 ml of water and once with 50 ml of brine. The organic layer was dried over anhydrous sodium sulfate, filtered, and evaporated to give a viscous, yellow oil that was purified by flash chromatography eluting with 1:1 ethyl acetate/dichloromethane to afford 1.35 g (92%) of the title product as a white solid. ^{1}H NMR (CDCl$_3$) δ 7.45-7.02 (14 H, m), 6.37-6.32 (1H, d), 4.78-4.72 (1H, m), 4.52-4.3 (3H, m), 3.82-3.77 (1H,m), 3.74 (3H, s), 3.03-2.87 (4H, m), 2.58-2.45 (2H, m), 2.45-2.35 (1H, m), 2.25-2.16 (1H, m).

[2-Oxo-5-(3-phenylpropionyl)-3-(3(S)-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]acetic acid (105b). [2-Oxo-5-(3-phenylpropionyl)-3-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]acetic acid methyl ester (**104b**; 680 mg, 1.32 mmol) was hydrolyzed by the procedure in example **105a** to afford 645 mg (98%) of the title compound as a white solid. ^{1}H NMR (CDCl$_3$) δ 7.58 (1H, br. s), 7.5-7.42 (1H, m), 7.35-6.95 (14H, m), 4.95-4.88 (1H, m), 4.64-4.55 (1H, d), 4.54-4.45 (1H, t), 4.15-4.05 (1H, d), 3.75 (1H, m), 3.05-2.75 (4H, m), 2.58-2.45 (2H, m), 2.45-2.28 (1H, m), 2.25-2.14 (1H, m).

2-Oxo-3(S)-{2-[2-oxo-5-(3-phenylpropionyl)-3(S)-(3-phenyl-propionyl-amino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]

acetylamino}butyric acid (106b). [2-Oxo-5-(3-phenylpropionyl)-3-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]acetic acid and 3-amino-4-oxobutyric acid tert-butylester

5   semicarbazone were coupled by the procedure in example 3, compound K (step A) to give 350 mg (85%) of a white solid. ^{1}H NMR (CDCl$_3$) δ 9.05 (1H, br. s), 7.58-7.55 (1H,d), 7.5-7.35 (1H, m), 7.35-6.95 (14 H, m), 6.75-6.72 (1H, d), 6.25 (1H, br. s), 5.25 (1H, br. s),

10   4.95-4.88 (1H, m), 4.8-4.72 (1H, m), 4.55-4.4 (2H, m), 3.92-3.88 (1H, d), 3.73-3.68 (1H, m), 2.95-2.8 (4H, m), 2.8-2.72 (1H, m), 2.62-2.55 (1H, m), 2.55-2.45 (2H, m), 2.4-2.32 (1H, m), 2.2-2.12 (1H, m), 1.45 (9H, s).

15   4-Oxo-3-{2-[2-oxo-5-(3-phenylpropionyl)-3-(3-phenyl-propionyl -amino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]-acetyl-amino}butyric acid tert-butyl ester semicarbazone was deprotected as described in example 3, compound K

20   (step C) to give 118 mg (47%) of the title compound as a white solid. ^{1}H NMR (CD$_3$OD) δ 7.48-6.95 (14 H, m), 4.65-4.15 (6H, m), 3.5-3.4 (1H, m), 2.85-2.72 (4H, m), 2.65-2.5 (1H, m), 2.5-2.34 (3H, m), 2.34-2.15 (2H, m).

[5-Benzyl-2-oxo-3(S)-(3-phenylpropionylamino)-2,3,4,5-
25   **tetrahydro -benzo[b][1,4]diazepin-1-yl]acetic acid** **methyl ester (104c).** [2-Oxo-3-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo-[b][1,4]diazepin-1-yl]acetic acid methyl ester (104a; 500 mg, 1.31 mmol), calcium carbonate (155 mg, 1.58

30   mmol), and benzyl bromide (170 µl, 1.44 mmol) were taken into 10 ml of dimethylformamide and heated to 80 °C for 8 hours. The mixture was diluted with 150 ml

of ethyl acetate and washed 4 times with 50 ml of
water. The organic layer was dried over anhydrous
sodium sulfate, filtered, and evaporated to give a
viscous, yellow oil that was purified by flash
chromatography eluting with dichloromethane/ethyl
acetate (8:2) to give 460 mg (75%) of the title
compound as a white solid. ^{1}H NMR (CDCl$_3$) δ 7.34-7.05
(14 H, m), 6.32-6.28 (1H, d), 4.84-4.76 (1H, d), 4.76-
4.70 (1H, m), 4.43-4.37 (1H, d), 4.26-4.18 (1H, d),
4.06-4.00 (1H, d), 3.79 (3H, s), 3.45-3.37 (1H, m),
3.02-2.95 (1H, m), 2.90-2.82 (2H, m), 2.5-2.34 (2H,
m).

[5-Benzyl-2-oxo-3(S)-(3-phenylpropionylamino)-2,3,4,5-
tetrahydro -benzo[b][1,4]diazepin-1-yl]acetic acid
(105c) was prepared by the hydrolysis of the ester
(102c) by the procedure reported in example 105a to
give 450 mg (98%) of the title compound as a white
solid: ^{1}H NMR (CD$_3$OD) δ 7.5-7.05 (14 H, m), 6.4 (1H,
br. s), 4.85-4.55 (2H,m), 4.5-4.21 (2H, m), 4.12-3.92
(1H, d), 3.45-3.3 (1H, m), 3.1-2.8 (3H, m), 2.55-2.28
(3H, m).

3(S)-{2-[5-Benzyl-2-oxo-3-(3(S)-phenylpropionylamino)-
2,3,4,5-tetrahydrobenzo[b][1, 4]diazepin-1-yl]-
acetylamino}-4-oxobutyric acid (106c). [5-Benzyl-2-
oxo-3(S)-(3-phenylpropionylamino)-2,3,4,5-tetrahydro-
benzo[b[1,4]diazepin-1-yl]acetic acid and 3(S)-amino-
4-oxobutyric acid tert-butylester semicarbazone were
coupled by the procedure in example 3, compound **K**
(step A) and to afford 260 mg (85%) of a white solid:
^{1}H NMR (CD$_3$OD) δ 7.35-7.0 (15 H, m), 4.94-4.88 (1H,
m), 4.68-4.58 (1H, d), 4.57-4.52 (1H, m), 4.41-4.34

(1H, d), 4.3-4.23 (1H, d), 4.1-4.04 (1H, d), 3.18-3.11
(1H, m), 3.09-2.98 (1H, m), 2.78-2.72 (2H, t), 2.65-
2.57 (1H, m), 2.42-2.33 (3H, m).

3(S)-{2-[5-Benzyl-2-oxo-3(S)-(3-phenylpropionylamino)-
2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]-
acetylamino}-4-oxobutyric acid tert-butyl ester
semicarbazone was deprotected as described in example
3, compound K (step C) to give 168 mg (81%) of the
title compound as a white solid. ^{1}H NMR (CD$_3$OD) δ
7.37-7.0 (14H, m), 4.75-4.62 (1H, m), 4.6-4.45 (2H,
m), 4.4-4.21 (2H, m), 4.15-3.95 (2H, m), 3.15-3.0 (2H,
m), 2.82-2.67 (2H, m), 2.65-2.52 (1H, m), 2.5-2.32
(3H, m).
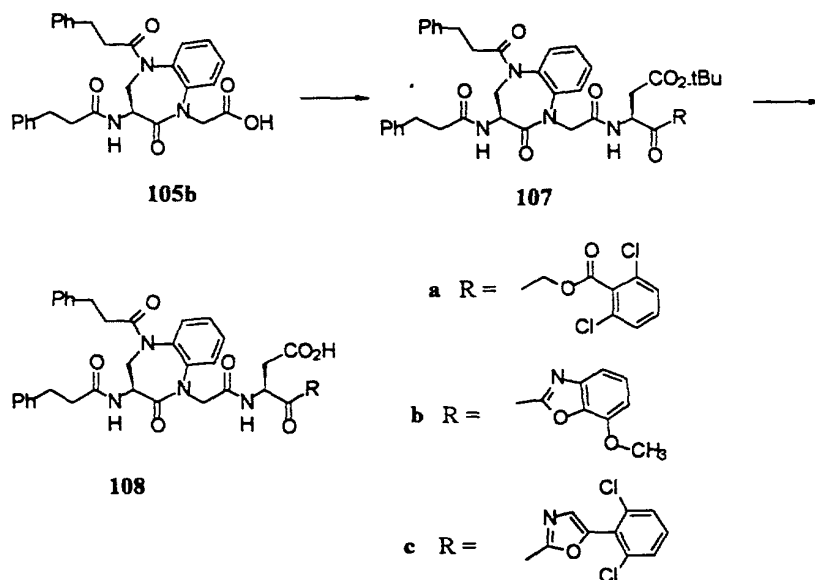
**2,6-Dichlorobenzoic acid 4-tert-butoxycarbonyl-2-oxo-
3(S)-{2-[2-oxo-5-(3-phenylpropionyl)-3(S)-(3-
phenylpropionylamino)-2,3,4,5-tetrahydro-
benzo[b][1,4]diazepin-1-yl]acetyl-amino}butyl ester
(107a).** The resulting semicarbazone was prepared by
the coupling of compound **105b** and t-butyl 3-

(allyloxycarbonylamino)-4-oxo-5-(2,6-dichlorobenzoyl-oxy)pentanoate (WO 93 16710) as described in compound **56a** to give 256 mg (58%) of the title compound as a white solid. ^{1}H NMR (CDCl$_3$) δ 7.45-
7.04 (17H, m), 6.45-6.34 (2H, m), 5.28-5.21 (1H, m), 5.1-5.0 (1H, m), 4.95-4.90 (1H, m), 4.75-4.70 (1H, m), 4.55-4.44 (1H, m), 4.32-4.22 (1H, dd), 3.99-3.85 (1H, dd), 3.85-3.76 (1H, m), 3.06-2.83 (5H, m), 2.83-2.74 (1H, m), 2.6-2.44 (2H, m), 2.43-2.33 (1H, m), 2.24-
2.15 (1H, m), 1.45 (9H, s).

2,6-Dichlorobenzoic acid 4-carboxy-2-oxo-3(S)-{2-[2-oxo-5-(3-phenylpropionyl)-3(S)-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]acetylamino}butyl ester (108a) was prepared from **107a** by the method described for compound **57a** which afforded 156 mg (68%) of the title compound as a white solid. ^{1}H NMR (CD$_3$OD) δ 7.5-6.9 (17H, m), 5.16-5.02 (1H, dd), 4.88-4.71 (2H, m), 4.62-4.44 (2H, m), 4.42-4.28 (2H, m), 4.27-4.18 (1H, m), 3.47-3.41 (1H, m), 2.90-2.60 (5H, m), 2.46-2.4 (2H, m), 2.39-2.18 (2H, m).

4-(7-Methoxybenzoxazol-2-yl)-4-oxo-3(S)-{2-[2-oxo-5-(3-phenylpropionyl)-3(S)-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b] [1,4]diazepin-1-yl]-acetylamino} butyric acid tert-butyl ester (107b).
4(R,S)-Hydroxy-4-(7-methoxybenzoxazol-2-yl)-3(S)-{2-[2-oxo-5-(3-phenylpropionyl)-3(S)-(3-phenylpropionylamino)-2,3,4,5-tetrahydro[b][1,4]diazepin-1-yl-acetylamino} butyric acid tert-butyl ester was prepared from **105b** and **66a** by the method described in example 5, compound **67** to

give 56% of a white solid: ^{1}H NMR (CDCl$_3$) δ 7.72-6.78 (19H, m), 6.37-6.28 (1H, m), 5.17-5.08 (0.5H, m), 4.92-4.82 (0.5H, m), 4.81-4.6 (1H, m), 4.6-4.35 ((3H,m), 4.05-3.9 (1H, m), 3.95 (3H, s), 3.82-3.7 (1H, m), 2.96-2.05 (10H, m), 1.45 (4.5H, s), 1.38 (4.5H, s).

The resulting product was converted to **107b** by the method described in example 5, compound **68a** to give the title compound (56%) as a white solid. ^{1}H NMR (CD$_3$OD) δ 7.62-6.8 (17H, m), 5.64-5.58 (0.5H, t), 5.52-5.46 (0.5H, t), 4.62-4.47 (2H, m), 4.40-4.32 (1H, m), 3.9 (1.5H, s), 3.88 (1.5 H, s), 3.43-3.37 (1H, m), 3.0-2.92 (1H, m), 2.90-2.62 (6H, m), 2.5-2.4 (2H, m), 2.28-2.15 (2H, m), 1.32 (4.5H, s), 1.25 (4.5H, s).

4-(7-Methoxybenzoxazol-2-yl)-4-oxo-3(S)-{2-[2-oxo-5-(3-phenylpropionyl)-3(S)-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]-acetylamino} butyric acid (108b) was prepared by the method described in example 5, compound **69a** to give the title compound (50%) as a white solid. ^{1}H NMR (CD$_3$OD) δ 7.41-6.88 (17H, m), 5.6-5.55 (0.5H, t), 5.48-5.43 (0.5H, t), 4.64-4.45 (2H, m), 4.45-4.30 (1H, m), 3.93 (1.5H, s), 3.90 (1.5H, s), 3.47-3.34 (1H, m), 3.10-2.85 (2H, m), 2.84-2.63 (5H, m), 2.6-2.4 (2H, m), 2.3-2.1 (2H, m).

4-[5-(2,6-Dichlorophenyl)oxazol-2-yl]-4-oxo-3(S)-{2-[2-oxo-5-(3- phenylpropionyl)-3(S)-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]-acetylamino} butyric acid tert-butyl ester (107c). 4-[5-(2,6-Dichlorophenyl)oxazol-2-yl]-4(R,S)-hydroxy-3(S)-{2-[2-

oxo- 5-(3-phenylpropionyl)-3(S)-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]-acetylamino} butyric acid tert-butyl ester was prepared from **106c** and **99** by a similar method as described for compound **67a** in example 5 to give 72% of a white solid. ^{1}H NMR (CDCl$_3$) δ 7.71-7.64 (1H, m), 7.58-7.42 (2H, m), 7.42-6.92 (15H, m), 6.5-6.37 (2H, m), 5.15-5.04 (1H, m), 4.88-4.68 (2H, m), 4.57-4.37 (2H, m), 4.28-4.13 (1H, m), 3.87-3.64 (2H, m), 3.04-2.80 (4H, m), 2.76-2.68 (1H, m), 2.67-2.42 (3H, m), 2.41-2.31 (1H, m), 2.22-2.12 (1H, m), 1.45 (9H, s).

The resulting product was converted to **107c** by a similar method as described for compound **68a** in example 5 to give the title compound in quantitative yield as a white solid. ^{1}H NMR (CDCl$_3$) δ 7.47-6.98 (18H, m), 6.52-6.42 (1H, d), 5.6-5.52 (1H, m), 4.78-4.71 (1H, m), 4.52-4.40 (2H, m), 4.03-3.94 (0.67H, m), 3.94-3.85 (0.33H, m), 3.85-3.75 (1H, m), 3.45-3.33 (1H, m), 3.08-2.98 (1H, m), 2.97-2.84 (4H, m), 2.55-2.43 (2H, m), 2.43-2.32 (1H, m), 2.23-2.13 (1H, m), 1.35 (9H, s).

4-[5-(2,6-Dichlorophenyl)oxazol-2-yl]-4-oxo-3(S)-{2-[2-oxo-5-(3- phenylpropionyl)-3(S)-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]-acetylamino} butyric acid (108c) was prepared from **107c** by a similar method as described for compound **69a** in example 5 to give 72% the title compound as a white solid. ^{1}H NMR (CD$_3$OD) δ 7.58-7.0 (18H, m), 5.62-5.53 (0.67H, m), 5.52-5.47 (0.33H, m), 4.68 (3H, m), 3.54-3.42 (1H, m), 3.1-2.92 (2H, m), 2.88-2.68 (5H, m),

2.63-2.45 (2H, m) 2.40-2.22 (2H, m).
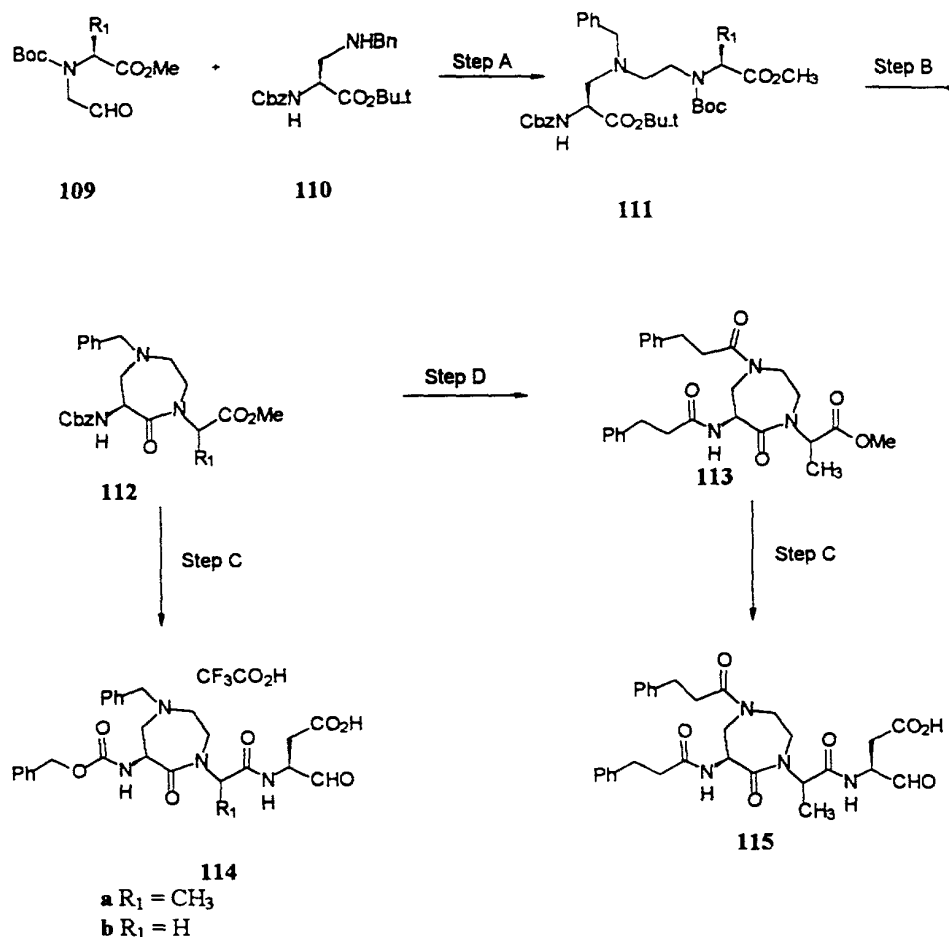
3(S)-{2(R,S)-[4-Benzyl-7-oxo-6(S)-(N-benzyloxycarbonylamino)-[1,4]diazepan-1-yl]-propionylamino}-4-oxo-butyric acid trifluoroacetic acid salt (114a):

Step A. To a solution of tert-butyl-2-N-benzyloxycarbonyl-3-N-benzyl-(S)-2,3-diaminopropionate (**110;** 0.85 g, 2.2 mmol), 3-(N-tert-butoxycarbonyl)amino-2-methyl-5-oxo-pentanoic acid methyl ester (**109a;** 0.65 g, 2.7 mmol), acetic acid (0.1 mL, 1.8 mmol), sodium acetate (0.36 g, 2

mmol) and 4 Å molecular sieves (1 g) in methanol (45
mL), was added sodium cyanoborohydride (0.33 g, 5.3
mmol). The mixture was stirred overnight at 25 °C
then filtered through Celite and concentrated under
5   reduced pressure. The residue was dissolved in 1 N
NaOH and extracted with ethyl acetate (3 x 40 mL).
The organic layer was dried (MgSO$_4$), filtered and
evaporated to give an oil. Chromatography (silica-
gel, 4:1 hexane: ethyl acetate as eluent) gave 0.92
10   g (68% yield) of **111a** as an oil.

Step B. The above material was dissolved in
dichloromethane (3 mL) cooled to 0 °C and treated
with a 25% solution of trifluoroacetic acid in
dichloromethane (20 mL) then allowed to warm to 25 °C
15   and stir until the reaction was judged complete by
TLC (4:1 hexane: ethyl acetate). The solvent was
removed under reduced pressure and the residue dried
under vacuum then dissolved in dichloromethane (40
mL) and treated with 4-methylmorpholine (1 mL, 9
20   mmol), HOBT (0.2g, 1.5 mmol) and EDC (0.61 g, 3.2
mmol). The resulting mixture was stirred overnight
at 25 °C then diluted with dichloromethane and washed
with water. The organic layer was dried (MgSO$_4$),
filtered and evaporated to give an oil.
25   Chromatography (silica-gel, 3:2 hexane: ethyl
acetate) gave 0.49 g (74% yield) of **112a** as a viscous
oil.

Step C. A solution of 2(R,S)-[4-benzyl-7-oxo-6(S)-
(N-benzyloxycarbonylamino)-[1,4]diazepan-1-yl]-
30   propionic acid methyl ester (**112a**; 0.15 g, 0.32 mmol)
was dissolved in methanol and treated with 1 M LiOH
(0.32 mL) and stirred 5.5 hours at 25 °C then
evaporated to dryness. The residue was azeotroped
with ethanol (2 x 10 mL), acetonitrile (2 x 10 mL),

benzene (2 x 10 mL) then dried under vacuum. The
resulting residue was converted to **114a** by a method
similar to that described in example 3, compound **K**
(steps A, B, and C) and purified by reverse phase
5   (C18 column) HPLC using 0.1%TFA:water/
0.1%TFA:acetonitrile as eluent. to give 17 mg (10%
yield) of a viscous oil: ^{1}H NMR (500 MHz, CD$_3$OD) δ
1.15 (m, 3 H), 2.30- 2.70 (m, 6 H), 2.72- 2.95 (bm, 6
H), 3.30- 3.80 (m, 4 H), 4.10 (m, 1 H), 4.40 (m, 4
10   H), 4.95 (m, 1H) 6.95- 7.10 (bs, 5 H), and 7.12- 7.20
ppm (bs, 5 H).

**3(S)-{2-[4-Benzyl-7-oxo-6(S)-(N-
benzyloxycarbonylamino)-[1,4]diazepan-1-yl]-
acetylamino}-4-oxo-butyric acid trifluoroacetic acid**
15   **salt (114b)** was prepared from **109b** by a similar
method described for the synthesis of **114a** to give
85 mg of viscous oil: ^{1}H NMR (500 MHz, CD$_3$OD) δ 1.20
(d, J = 7 Hz, 3 H), 2.28 (m, 2 H), 2.60 (m, 2 H),
3.18 (bs, 6 H), 3.35- 3.45 (m, 2 H), 3.60- 3.95 (m, 2
20   H), 4.15 (m, 1 H), 4.32 (m, 1 H), 4.42 (m, 1 H), 5.00
(bm, 2 H), 7.20 (bs, 5 H), and 7.40 ppm (bs, 5 H); ^{19}F
NMR (470 MHz, CD$_3$OD) δ -10.72 ppm (s, 3 F).

**4-Oxo-3(S)-{2(R,S)-[7-oxo-4-(3-phenyl-propionyl)-
6(S)-(3-phenyl-propionylamino)-[1,4]diazepan-1-yl]-**
25   **propionylamino}-butyric acid (115):**
Step D.   A suspension of 2(R,S)-[4-benzyl-7-oxo-
6(S)-(N-benzyloxycarbonylamino)-[1,4]diazepan-1-yl]-
propionic acid methyl ester (**112b**; 0.22 g, 0.49 mmol)
and 20% Pd(OH)$_2$ on carbon (50 mg) in ethanol was
30   stirred under hydrogen atmosphere for 7 hours. The
solvent was evporated under reduced pressure and the

residue dissolved in dichloromethane (20 mL) then
treated with triethylamine (1 mL) and
dihydrocinnamoyl chloride (170 mg, 1 mmol). The
resulting mixture was allowed to stir overnight then

5   diluted with ethyl acetate and washed with 1 N NaOH.
The organic layer was dried (MgSO$_4$), filtered and
evaporated to give an oil. Chromatography (silica-
gel, 4:1 hexane: ethyl acetate) gave 0.175 g (75%
yield) of **113** as an oil.

10   **Step C.** A 0.15 g sample of **113** (0.32 mmol) was
dissolved in methanol, treated with 1 M LiOH (0.32
mL), stirred at 40 °C overnight then evaporated to
dryness. The residue was azeotroped with ethanol (2
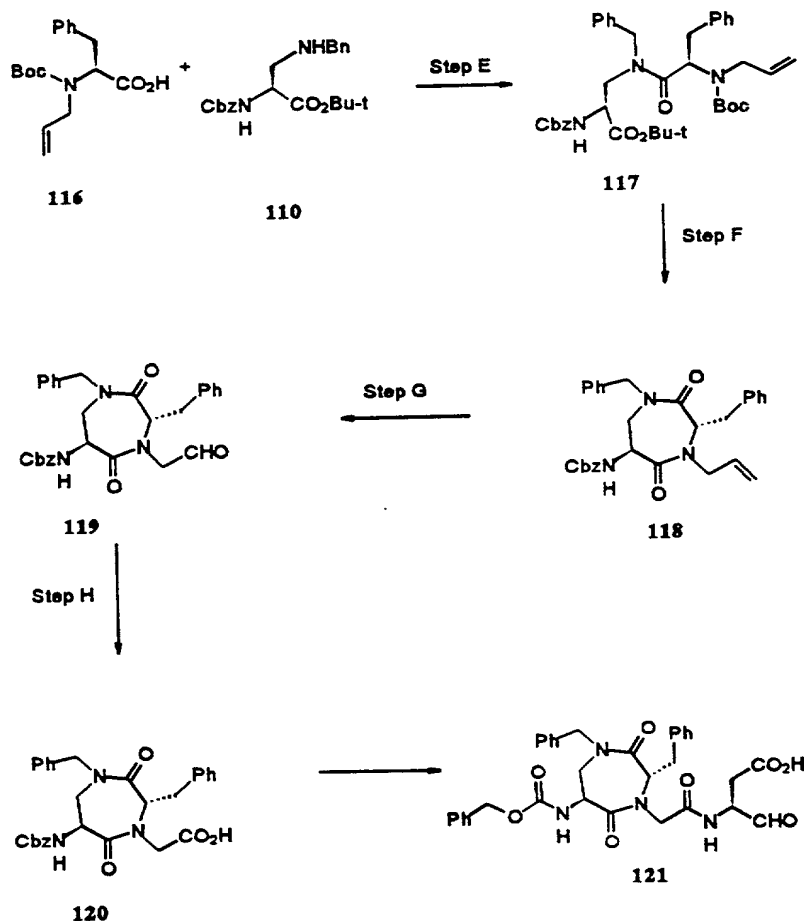x 10 mL), acetonitrile (2 x 10 mL), benzene (2 x 10

15   mL) then dried under vacuum. The resulting residue
was converted to **115** by a method similar to that
described in example 3, compound **K** (steps A, B,and
C).

20

3-{2-[2,4-Dibenzyl-3,7-dioxo-6-(N-
benzyloxycarbonylamino)-[1,4]diazepan-1-yl]-
acetylamino}-4-oxo-butyric acid (121):

Step E. A solution of tert-butyl-2-N-carbobenzoxy-3-
N-benzyl-(S)-2,3-diaminopropionate (110; 1.77 g, 4.6
mmol), N-allyl-N-tert-butoxycarbonyl-(S)-
phenylalanine (116; 1.04 g, 4.8 mmol), HOBT (0.74 g,
5.5 mmol) and EDC (1.33 g, 6.9 mmol) in
dichloromethane (50 mL) was allowed to stirr at 25 °C
for 16 h then diluted with dichloromethane (100 mL)
and washed with water. The organic layer was dried
(MgSO₄), filtered and evaporated to give an oil.
Chromatography (silica-gel, 85: 15 hexane: ethyl

acetate) gave 1.34 g (43% yield) of **117** as a
colorless viscous oil.

Step F. A 1.34 g sample of **117** was dissolved in
dichloromethane (3 mL) and treated with a 50%
5   solution of trifluoroacetic acid in dichloromethane
(20 mL). After 1.5 h, the solvent was removed under
reduced pressure and the residue dried under vacuum
then dissolved in dichloromethane (50 mL) and
combined with 4-methylmorpholine (0.2 mL, 2 mmol),
10   HOBT (0.27 g, 2 mmol) and EDC (0.8 g, 4 mmol). The
mixture was stirred overnight at 25 °C then diluted
with dichloromethane and washed with water. The
organic layer was dried (MgSO$_4$), filtered and
evaporated to give an oil. Chromatography (silica-
15   gel, 7:3 hexane: ethyl acetate) gave 0.8 g (80%
yield) of **118** as a viscous oil.

Step G. A 0.8 g sample of **118** was dissolved in
methanol (40 mL), cooled to -78 °C and saturated with
ozone until the solution was blue in color. The
20   excess ozone was removed by purging with argon then
dimethylsulfide (5 mL) was added and the mixture
allowed to warm to 25 °C and stir 3 h. Solvent
removal and chromatography (silica-gel, 1:1 hexane:
ethyl acetate) gave 0.74 g (74% yield) of **119** as a
25   white solid.

Step H. A 0.2 g sample (0.4 mmol) of **119** was
dissolved in acetone (25 mL), cooled to 0 °C and
treated dropwise with a solution of Jones reagent
until the orange color persisted. 2-Propanol (5 mL)
30   was then added to the mixture and the resulting
soltuion filtered through Celite and washed with
acetone. Solvent removal gave a green-white solid
that was dried under vacuum to give **120**. The
resulting residue was converted to **121** by a method

similar to that described in example 3, compound K
(steps A, B, and C). Chromatography (SiO_2, 95: 4.5:
0.5 dicholormethane: methanol: acetic acid eluent)
gave 85 mg (53% yield) of cream colored solid which
was identified as 3-{2-[2,4-dibenzyl-3,7-dioxo-6-(N-
benzyloxycarbonylamino)-[1,4]diazepan-1-yl-
acetylamino}-4-oxo-butyric acid (121) on the basis of
the following spectral data: ^1H NMR (500 MHz, CD_3OD)
δ 2.38 (m, 1 H), 2.45 (m, 1 H), 3.21 (bs, 2 H), 3.32-
3.39 (bm, 6 H), 3.85 (m, 1 H), 4.05 (m, 1 H), 4.21
(bm, 1 H), 4.31 (bs, 1 H), 4.45 (dm, J = 11 Hz, 1 H),
4.95 (bs, 4 H), 7.20 (bs, 5 H), and 7.33- 7.45 ppm
(m, 5 H); ^{19}F NMR (470 MHz, CD_3OD) d -10.62 ppm (s, 3
F).
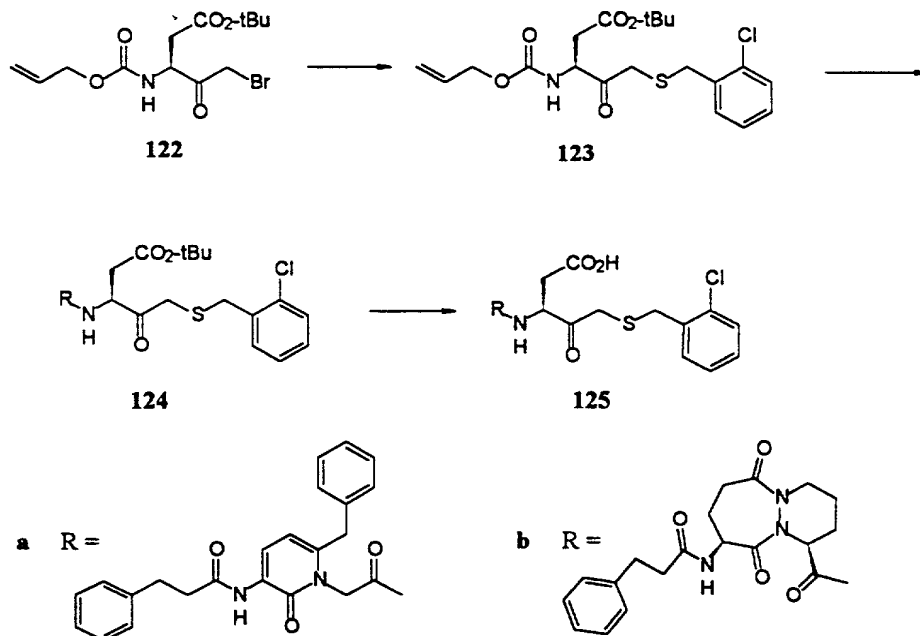
**t-Butyl (3S) N-(allyloxycarbonyl)-3-amino-5-(2-
chlorophenylmethylthio)-4-oxo-pentanoate (123).**
Potassium fluoride (273mg, 4.70mmol) and then 2-
chlorophenylmethyl thiol (373mg, 2.35mmol) were added

to a stirred solution of (3S) t-butyl N-(allyloxycarbonyl)-3-amino-5-bromo-4-oxo-pentanoate (**122**; 749mg, 2.14mmol; WO 93 16710) in dimethylformamide (20ml). The mixture was stirred for 3.5h, quenched with water (50ml) and extracted with ethyl acetate (2 x 50ml). The combined organic extracts were washed with water (4 x 50ml) then brine (50ml). They were dried (MgSO$_4$) and concentrated to afford an oil which was purified by flash chromatography (10-35% ethyl acetate / hexane) to afford 832 mg (91%) of a colourless solid: mp. 45-6 °C; [α]$_D^{20}$ -19.0° (c 1.0, CH$_2$Cl$_2$); IR (film) 3340, 2980, 2935, 1725, 1712, 1511, 1503, 1474, 1446, 1421, 1393, 1368, 1281, 1244, 1157, 1052, 1040, 995, 764, 739; ^{1}H NMR (CDCl$_3$) δ 7.36 (2H, m), 7.21 (2H, m), 5.91 (2H, m), 5.27 (2H, m), 4.76 (1H, m), 4.59 (2H, d), 3.78 (2H, s), 3.36 (2H, m), 2.91 (1H, dd), 2.74 (1H, dd), 1.43 (9H, s). Anal. Calcd for C$_{20}$H$_{26}$ClNO$_5$S: C, 56.13; H, 6.12; N, 3.27; S, 7.49. Found: C, 56.08; H, 6.11; N, 3.26; S, 7.54. MS (C.I.) 430/28 (M$^+$ + 1, 3%), 374/2 (100).

t-Butyl (3S) 3(2(6-benzyl-1,2-dihydro-2-oxo-3(3-phenylpropionylamino)-1-pyridyl)acetylamino-5-(2-chlorophenylmethylthio)-4-oxopentanoate (124a). 6-Benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionylamino)-pyridyl acetic acid (**52b**; 300mg, 0.76mmol) in THF (7ml) was stirred with 1-hydroxybenzotriazole (205mg, 1.52mmol) and 1-(3-dimethylaminopropy-3-ethylcarbodiimide hydrochloride). After 3 min, water (12 drops) was added and the mixture stirred 10min then treated with t-butyl (3S) N-(allyloxycarbonyl)-3-amino-5-(2-chlorophenylmethylthio)-4-oxopentanoate

(**123**) (325mg, 0.76mmol), bis (triphenylphosphine) palladium II chloride (20mg) and tributyltin hydride (0.6ml, 2.28mmol). The mixture was stirred for 5h at room temperature, poured into ethyl acetate and washed with aqueous 1M HCl (x2), aqueous sodium bicarbonate, brine, dried (MgSO$_4$) and concentrated. The residue was triturated with pentane and the supernatant discarded. Chromatography (silica gel, 50% ethyl acetate/hexane) afforded a colourless foam (439mg, 81%): $[\alpha]_D^{21}$ -18.3 ° (c 0.5, CH$_2$Cl$_2$); IR (KBr) 3356, 3311, 1722, 1689, 1646, 1599, 1567, 1513, 1367, 1154; ^{1}H NMR (CDCl$_3$) δ 8.39 (1H, d), 8.23 (1H, s), 7.24 (14H, m), 6.16 (1H, d), 4.95 (1H, m), 4.63 (2H, m), 4.02 (2H, s), 3.74 (2H, s), 3.27 (2H, s), 2.85 (6H, m), 1.40 (9H, s). Anal. Calcd for C$_{39}$H$_{42}$ClN$_3$O$_6$S: C, 65.39; H, 5.91; N, 5.87. Found: C, 65.51; H, 5.99; N,5.77.

t-Butyl[3S(1S,9S)]-3-(6,10-dioxo-1,2,3,4,7,8,9,10-octahydro)-9-(3-phenylpropionylamino)-6H-pyridazine[1,2-a][1,2]diazepine-1-carboxamido-5-(2-chlorophenylmethylthio)-4-oxopentanoate (124b) was prepared by a similar method as **124a** from the thioether **123** and 3S(1S,9S)-3-(6,10-dioxo-1,2,3,4,7,8,9,10-octahydro)-9-(3-phenylpropionylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylic acid (**45a**) to afford 452mg (50%) of colourless foam: mp 55-7 °C; $[\alpha]_D^{22}$ -94.0° (c 0.12, CH$_2$Cl$_2$); IR (KBr) 3288, 2934, 1741, 1722, 1686, 1666, 1644, 1523, 1433, 1260, 1225, 1146, 757; ^{1}H NMR (CDCl$_3$) δ 7.35 (3H, m), 7.20 (7H, m), 6.46 (1H, d), 5.21 (1H, m), 4.97 (2H, m), 4.56 (1H, m), 3.75 (2H, s), 3.25 (3H, m), 2.93 (5H, m), 2.71 (1H,

dd), 2.55 (2H, m), 2.30 (1H, m), 1.92 (3H, m), 1.66 (2H, m), 1.42 (9H, s). Anal. Calcd for $C_{35}H_{43}ClN_4O_7S$. $0.25H_2O$: C, 59.73; H, 6.23; Cl, 5.04; N, 7.96; S, 4.56. Found: C, 59.73; H, 6.19; Cl, 5.10; N, 7.79; S, 4.58. MS (-FAB) 697 (M-1, 100).

(3S) 3(2(6-Benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionylamino)-1-pyridyl)acetylamino-5-(2-chlorphenylmethylthio)-4-oxopentanoic acid (125a). t-Butyl-3(2(6-benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionylamino)-1-pyridyl)acetyl-amino-5-(2-chlorophenylmethylthio)-4-oxopentanoate (**124a**) (400mg, 0.56mmol) in dichloromethane (3ml) at 0 °C was treated with trifluoroacetic acid (3ml) and stirred at 0 °C for 1h and room temperature for 0.5h. The solution was concentrated then redissolved in dichloromethane and reconcentrated. This procedure was repeated three times. The residue was stirred in ether for 1hr and filtered to yield a colourless solid (364mg, 99%): mp. 165-7 °C; $[\alpha]_D^{22}$ -27.7 ° (c 0.2, CH_2Cl_2); IR (KBr) 3289, 1712, 1682, 1657, 1645, 1593, 1562, 1527, 1497, 1416, 1203, 1182; ^{1}H NMR (CDCl$_3$) d 8.47 (1H, d), 8.21 (1H, s), 7.70 (1H, d), 7.22 (14H, m), 6.24 (1H, d), 5.03 (1H, m), 4.65 (2H, m), 4.06 (2H, s), 3.69 (2H, m), 3.23 (2H, m), 2.88 (6H, m).

[3S(1S, 9S)]-3-(6,10-dioxo-1,2,3,4,7,8,9,10-octahydro)-9-(3-phenylpropi onyl-amino)-6H-pyridazine[1,2-a][1,2]diazepine-1-carboxamido-5-(2-chlorophenyl-methylthio)-4-oxopentanoic acid (125b), was prepared by a similar method as **125a** from the t-butyl ester **124b** to afford

362mg (93%) of colourless powder: mp 76-80 °C; $[\alpha]_D^{21}$ -134 ° (c 0.10, MeOH); IR (KBr) 3309, 2935, 1725, 1658, 1528, 1445, 1417, 1277, 1219, 1175; ^{1}H NMR (D_6-DMSO) δ 8.80 (1H, d), 8.19 (1H, d), 7.31 (9H, m), 5.09 (1H, m), 4.74 (1H, m), 4.63 (1H, m), 4.35 (1H, m), 3.76 (2H, m), 3.28 (3H, m), 2.80 (5H, m), 2.52 (4H, m), 2.16 (2H, m), 1.90 (3H, m). Anal. Calcd for $C_{31}H_{35}Cl_2N_4O_7S$. $0.25H_2O$: C, 57.49; H, 5.53; N, 8.65; S, 4.95. Found: C, 57.35; H, 5.43; N, 8.45; S, 4.88. MS (-FAB) 641 (M-1, 100).

The data of the examples above demonstrate that compounds according to this invention display inhibitory activity towards IL-1ß Converting Enzyme.

Insofar as the compounds of this invention are able to inhibit ICE in vitro and furthermore, may be delivered orally to mammals, they are of evident clinical utility for the treatment of IL-1 mediated diseases. These tests are predictive of the compounds ability to inhibit ICE in vivo.

While we have described a number of embodiments of this invention, it is apparent that our basic constructions may be altered to provide other embodiments which utilize the products and processes of this invention. Therefore, it will be appreciated that the scope of this invention is to be defined by the appended claims, rather than by the specific embodiments which have been presented by way of example.